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(54)【発明の名称】　ポリスルホン系中空糸型血液浄化膜とその製造方法

(57)【要約】

【課題】　生体適合性を改良し、中空糸内表面側にポリビニルピロリドンの溶出が極めて少なく、さらに、分離特性を改良したポリスルホン系血液浄化膜を提供する。

【解決手段】　実質的に分離機能を有する選択分離層が中空糸膜内表面側に存在し、かつ、ポリビニルピロリドンが１ないし１０重量%含有されており、該ポリビニルピロリドンの５ないし５０%が水に可溶性であり、かつ、内表面のポリビニルピロリドンの濃度が３０%から４５%の範囲にあるポリスルホン系中空糸型血液浄化膜。

【効果】　本発明のポリスルホン系中空糸型血液浄化膜は、血液適合性を改良し、血液側へのポリビニルピロリドンの溶出量が極めて少なく、さらに、分子量分画性の優れた中空糸膜である。この発明により、これからの透析治療において非常に有意義な人工腎臓を提供することができる。

【特許請求の範囲】

【請求項１】　実質的に分離機能を有する選択分離層が中空糸膜内表面側に存在し、かつ、ポリビニルピロリドンを含有するポリスルホン系中空糸型血液浄化膜において、ポリビニルピロリドンが１～１０重量%含有されており、該ポリビニルピロリドンの５～５０%が水に可溶性であり、かつ、中空糸膜内表面におけるポリビニルピロリドンの濃度が３０%から４５%の範囲にあることを特徴とするポリスルホン系中空糸型血液浄化膜。

【請求項２】　中空糸内表面におけるポリビニルピロリドンの濃度が３３%から４０%である請求項１記載のポリスルホン系中空糸型血液浄化膜。

【請求項３】　中空糸膜内側を４０%アルコール水溶液で循環抽出した時のポリビニルピロリドンの溶出量が膜面積１m^2 当たり０．５ｍｇ以下であることを特徴とする請求項１記載のポリスルホン系中空糸型血液浄化膜。

【請求項４】　中空糸膜内表面に０．８μｍ以上の引き裂かれた間隙を有しないことを特徴とする請求項１記載のポリスルホン系中空糸型血液浄化膜。

【請求項５】　選択分離層の厚さが２～１５μｍであることを特徴とする請求項１記載のポリスルホン系中空糸型血液浄化膜。

【請求項６】　ポリスルホン系ポリマーを１５～２０重量%含有し、かつ、ポリスルホン系ポリマーに対するポリビニルピロリドンの重量比率が０．２５～０．５であるポリマー溶液を用いて中空糸膜を紡糸した後、物理化学的な方法により該中空糸膜中のポリビニルピロリドンの一部を不溶化させることを特徴とするポリスルホン系中空糸型血液浄化膜の製造方法。

【請求項７】　紡糸後の中空糸膜を飽和含水率以上の湿潤状態とした後、放射線を照射してポリビニルピロリドンの一部を不溶化させることを特徴とする請求項６記載のポリスルホン系中空糸型血液浄化膜の製造方法。

【請求項８】　紡糸後の中空糸膜を、ポリスルホン系ポリマーの良溶媒と貧溶媒の混合溶剤であってポリビニルピロリドンを溶解する溶剤又はアルコール系溶剤でポリビニルピロリドンを抽出して洗浄することを特徴とする請求項６記載のポリスルホン系中空糸型血液浄化膜の製造方法。

【請求項９】　ポリスルホン系ポリマーの良溶媒がジメチルアセトアミドまたは／およびジメチルスルホキシドであり、ポリスルホン系ポリマーの貧溶媒が水であることを特徴とする請求項８記載のポリスルホン系中空糸型血液浄化膜の製造方法。

【請求項１０】　紡糸後の中空糸膜を１３０～１６０℃のアルコール系溶剤で抽出洗浄することを特徴とする請求項６記載のポリスルホン系中空糸型血液浄化膜の製造方法。

【請求項１１】　アルコール系溶剤がグリセリンであることを特徴とする請求項１０記載のポリスルホン系中空糸型血液浄化膜の製造方法。

【請求項１２】　ポリスルホン系ポリマーおよびポリビニルピロリドンを、これらの共通溶剤に溶解した粘度が１５００～６０００ｍＰａ・秒の紡糸原液を、ドラフト率１．１～１．９、吐出線速度９０ｍ／ｍｉｎ以下で紡糸することを特徴とする請求項６記載のポリスルホン系中空糸型血液浄化膜の製造方法。

【発明の詳細な説明】

【０００１】

【発明の属する技術分野】本発明は、ポリスルホン系中空糸型血液浄化膜およびその製造方法に関するものである。詳しくは、血液適合性と分離特性が改良されたポリスルホン系血液浄化膜およびその製造方法に関するものである。

【０００２】

【従来の技術】近年、選択透過性分離膜を用いた分離技術である限外濾過法、逆浸透法、気体分離法等が各種の分野において実用化されており、その多様な用途に各々適する素材から作られた分離膜が市販されている。選択透過性分離膜の素材としては、セルロース系、セルロースアセテート系、ポリアミド系、ポリアクリロニトリル系、ポリビニルアルコール系、ポリメチルメタクリレート系、ポリスルホン系、ポリオレフィン系などのポリマーが使用されている。中でもポリスルホン系ポリマーは、耐熱性、耐酸性、耐アルカリ性、耐酸化性などの物理化学的性質が優れていることから、近年の医療用、工業用分離膜素材として注目されている。

【０００３】しかし、ポリスルホン系ポリマーは疎水性の素材であるために、これを素材とした選択透過性分離膜は、親水性ポリマーを素材とした選択透過性分離膜に比べて水濡れ性がよくない。このため、医療用とした場合、血漿蛋白の吸着が起こりやすく、気泡の抜けが悪いため膜中に残った気泡が血中へ抜け出し、血小板を活性化することで血液凝固に至るという欠点が指摘されている。

【０００４】そこで、ポリスルホン系ポリマーから成る選択透過性分離膜に親水性を付与して水濡れ性を向上させるための検討がなされ、そのひとつの方法として、ポリスルホン系ポリマーに親水性ポリマーを含有させた選択透過性分離膜とその製法が提案されている。しかし、親水性ポリマーの含有量が少ないと水濡れ性が悪くなり、血液凝固を引き起こし、反対に親水性ポリマーの含有量が多いと、製膜後の膜からの親水性ポリマーの溶出量が多くなるという問題点がある。

【０００５】特開昭６１－２３８３０６号、同６３－９７６６６号には、ポリスルホン系ポリマー、親水性ポリマー、該ポリスルホン系ポリマーに対して非溶媒もしくは膨潤剤なる添加剤を加えた系を製膜原液として用いたポリスルホン系分離膜の製造方法が開示されているが、親水性ポリマーの溶出を低減させる方法の記載はない。

また、特開昭６３－９７２０５号、同６３－９７６３４号、特開平４－３００６３６号には、上記方法で製造されたポリスルホン系分離膜を放射線処理および／または熱処理を施すことによって親水性ポリマーを不溶化し、親水性ポリマーの溶出を低減させる方法が開示されている。しかし、この架橋により親水性ポリマーが不溶化するためか、血液適合性が悪くなる。

【０００６】特開平６－１６５９２６号では、ポリグリコール類とビニルピロリドン系ポリマーを含有するポリスルホン系中空糸膜を水洗、熱水洗処理、該ポリスルホン系ポリマーに対して貧溶媒作用を有する溶液での処理を行ない、中空繊維膜を製造する方法が開示されている。しかし、この貧溶媒作用を有する溶剤での処理は９０℃で行われており、抽出除去が十分ではない。

【０００７】紡糸ドラフトに関しては、特公平５－５４３７３号に疎水性ポリマー、親水性ポリマーおよびそれらの共通溶媒からなる低粘度の原液を紡糸して製造された、親水性ポリマーを１～１０重量%含有し、かつ、３～１０%の吸水能力を有する血液処理用の中空繊維の製法が開示されており、この中で、紡糸組成物の紡糸口金から出る速度および生成された繊維の引き取り速度が同じこと、すなわち、紡糸ドラフト率が１であることが好ましいとある。しかし、実際にドラフト率が１の場合、紡速をあげることが難しい。紡速を上げるために原液の吐出量を上げると、紡糸口金の圧損が大きくなること、紡糸原液の吐出線速度が増大し、紡糸原液の吐出むらが生じ易くなり、紡糸が不安定になること、および膜構造が乱れることなどの問題が起こる。また、特開平６－１６５９２６号には、極端にノズルドラフトを大きくしたり、小さくすると構造が不安定になるので、ノズルドラフトは通常２～５の範囲に設定される、とあるが、ドラフト率が２を越えると中空糸内表面が引き裂かれた構造となり、有用蛋白であるアルブミンがリークしやすくなるなどの問題点が指摘される。

【０００８】近年、透析合併症の原因として、β_2－ミクログロブリン（β_2－MG）等の低分子蛋白が挙げられ、これらを血液から効率よく除去できる高性能な透析膜が望まれている。上記した従来の技術では、分画性に対する十分な検討がなされておらず、必ずしも満足いくものではない。すなわち、低分子蛋白の除去を良くしようと膜の透過性能を上げると、アルブミンなどの有用蛋白のリークが問題となるからである。

【０００９】

【発明が解決しようとする課題】本発明は、従来技術の問題点を解消し、血液適合性を改良し、中空糸膜の内表面側へのポリビニルピロリドンの溶出が極めて少なく、しかも、膜の分離特性を改良したポリスルホン系血液浄化膜およびその製造方法を提供することを目的とする。

【００１０】

【課題を解決するための手段】本発明者らは、上記課題を達成すべく鋭意検討した結果、ポリビニルピロリドン（以下、ＰＶＰという）を含有する中空糸状ポリスルホン系中空糸型血液浄化膜において、ＰＶＰの一部を水に不溶な状態とし、かつ、中空糸膜内表面のＰＶＰ濃度を適切にすることにより、内表面からのＰＶＰの溶出が少なく、血液適合性に優れ、しかも、清浄な中空糸膜を提供できることを見い出した。また、適切な溶剤でＰＶＰを抽出することにより中空糸膜を洗浄し、内表面からのＰＶＰの溶出がさらに少ない、清浄な中空糸膜を提供できることを見い出した。さらに、適切な粘度を有する紡糸原液から、適切な紡糸ドラフト率で紡糸することにより、膜中で実質的に溶質分子をふるい分ける効果を持つ選択分離層の厚さを適切に制御できるとともに、中空糸膜内表面に引き裂き構造がなく、不要物質の除去、有用物質の回収を効率良く行うことのできる分画性のシャープなポリスルホン系血液浄化膜を提供できることを見い出した。

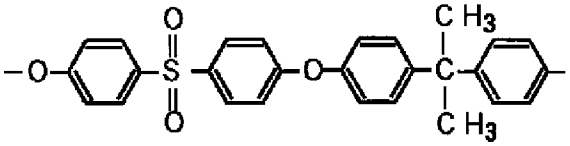
【００１１】すなわち、本発明は、実質的に分離機能を有する選択分離層が中空糸膜内表面側に存在し、かつ、ポリビニルピロリドンを含有するポリスルホン系中空糸型血液浄化膜において、ポリビニルピロリドンが１ないし１０重量%含有されており、該ポリビニルピロリドンの５ないし５０%が水に可溶性であり、かつ、内表面のポリビニルピロリドンの濃度が３０%から４５%の範囲にあることを特徴とするポリスルホン系血液浄化膜である。

【００１２】本発明はまた、ポリスルホン系ポリマーを１５～２０重量%含有し、かつ、ポリスルホン系ポリマーに対するポリビニルピロリドンの重量比率が０．２５～０．５であるポリマー溶液を用いて中空糸膜を紡糸した後、物理化学的な方法により該中空糸膜中のポリビニルピロリドンの一部を不溶化させることを特徴とするポリスルホン系中空糸型血液浄化膜の製造方法である。

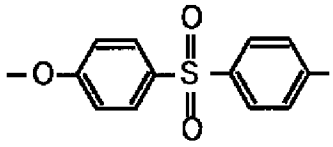
【００１３】本発明はさらに、紡糸後の中空糸膜を、ポリスルホン系ポリマーの良溶媒と貧溶媒の混合溶剤であってポリビニルピロリドンを溶解する溶剤またはアルコール系溶剤でポリビニルピロリドンを抽出して洗浄することを特徴とするポリスルホン系血液浄化膜の製造方法、および、ポリスルホン系ポリマーおよびポリビニルピロリドンをこれらの共通溶剤に溶解した粘度が１５００～６０００ｍＰａ・秒の紡糸原液を、ドラフト率１．１～１．９、吐出線速度９０ｍ／ｍｉｎ以下で紡糸することを特徴とするポリスルホン系中空糸型血液浄化膜の製造方法である。以下に本発明を詳細に説明する。

【００１４】本発明で言うポリスルホン系ポリマーとは、スルホン結合を有する高分子結合物の総称であり特に限定されるものでないが、例を挙げると

【化１】



【化２】



に示される繰り返し単位をもつポリスルホン系ポリマー樹脂が広く市販されており、入手も容易なため好ましく用いられる。前者の構造を持つポリスルホン樹脂は、アモコ・パフォーマンス・プロダクツ社より「ユーデル」の商標名で、また、ビー・エー・エス・エフ社より「ウルトラゾーン」の商標名で市販されており、重合度等によっていくつかの種類が存在する。

【００１５】また、本発明のＰＶＰは、Ｎ－ビニルピロリドンをビニル重合させた水溶性の高分子化合物であり、アイ・エス・ピー社より「プラスドン」の商標名で、また、ビー・エー・エス・エフ社より「コリドン」の商標名で市販されており、それぞれいくつかの分子量のポリビニルピロリドンがある。中空糸膜中のＰＶＰ含有量が低いと、血液に接触する中空糸膜内表面のＰＶＰ濃度が上がらず膜の親水性が悪くなるため、血液と接触した際、血液凝固が起こり易くなる。また、後述するように、中空糸膜中のＰＶＰ含有量を大きくするには、紡糸に使用するポリマー溶液中のＰＶＰ濃度を高くすればよいが、ポリマー溶液の粘度も上がり紡糸が不能となる。このため、本発明では中空糸膜中にＰＶＰは１～１０重量%の範囲で中空糸膜に含有される。好ましくは２．５～８重量%の範囲である。

【００１６】中空糸膜中のＰＶＰ含有量は、窒素およびイオウの元素分析値により容易に算出できる。また、中空糸膜を熱分解ガスクロマトグラフィーで分析し、ＰＶＰ由来のピークを解析することによっても容易に求めることができる。ＰＶＰは水に溶けやすいポリマーであり、中空糸膜から水や血液に容易に溶出する。含有されるＰＶＰをすべて不溶化すると、中空糸膜からの溶出は完全になくなるが、膜表面の親水化効果も弱くなる。このため本発明では、ＰＶＰの一部を架橋により不溶化させ、水に可溶性のＰＶＰは、中空糸膜に含有される全量の５ないし５０％である。この範囲にあると中空糸膜からの溶出も抑えられ、膜表面の親水化効果も維持される。

【００１７】水に可溶性のＰＶＰ量は、架橋によって不溶化していない膜中のＰＶＰ量であって、次のようにして求められる。すなわち、中空糸膜をＮ－メチル－２－ピロリドンで完全に溶解させる。次いで、このポリマー溶液に水を添加してポリスルホン系ポリマーを沈殿させる。静置後、得られる上清液中のＰＶＰ量を液体クロマトグラフィーで定量する。中空糸膜の血液適合性に重要な因子は、膜表面の親水性であり、ＰＶＰを含有するポリスルホン系中空糸膜では、膜内表面のＰＶＰ濃度が重要である。表面ＰＶＰ濃度が低すぎると膜表面が疎水性を示し、血漿蛋白が吸着しやすく、血液の凝固も起こりやすい。すなわち、血液適合性が不良となる。逆に表面ＰＶＰ濃度が高すぎると、ＰＶＰの血液等への溶出量が増加し、本発明の目的や用途にとって好ましくない結果を与える。したがって、本発明での膜内表面ＰＶＰの濃度は、３０%～４５%の範囲であり、好ましくは３３%～４０%である。

【００１８】中空糸膜内表面のＰＶＰ濃度は、Ｘ線光電子分光（ＥＳＣＡ）によって決定される。すなわち、中空糸膜内表面のＥＳＣＡの測定は、試料を両面テープ上に並べた後、カッターで繊維軸方向に切開し、中空糸膜の内側が表になるように押し広げたものを並べて試料とし、通常の方法で測定する。すなわち、Ｃ１ｓ、Ｏ１ｓ、Ｎ１ｓ、Ｓ２ｐスペクトルの面積強度より、装置付属の相対感度係数を用いて窒素の表面濃度（Ａ）とイオウの表面濃度（Ｂ）を求め、

表面ＰＶＰ濃度＝Ａ×１００／（Ａ×１１１＋Ｂ×４４２）

より表面ＰＶＰ濃度を算出する。

【００１９】本発明では、中空糸膜からのＰＶＰの溶出は、中空糸膜内面を４０%エタノール水溶液で循環抽出したときの溶出量で評価される。具体的には、中空糸膜をモジュールに組み込み、血液側に４０%エタノール水溶液を３７℃で４時間循環して、抽出されるＰＶＰ量を測定することにより評価される。抽出媒体として、３７℃の血液が適切であるが、溶出する親水性高分子が微量すぎ、また、妨害物質が多いため、抽出されるＰＶＰの定量が難しい。また、抽出媒体としては、水も抽出力が弱く、抽出されるＰＶＰの定量が難しい。４０%エタノール水溶液が、抽出媒体として適切である。

【００２０】本発明では、上述のようにＰＶＰの一部を架橋により不溶化させ、中空糸膜からの溶出が抑制される。さらに、本発明では、中空糸膜からのＰＶＰの溶出が抑制され、中空糸膜内側を４０%アルコール水溶液で循環抽出した時のポリビニルピロリドンの溶出量が、膜面積１m^2 当たり０．５ｍｇ以下であることがより好ましい。このような中空糸膜は、以下のようにして得ることができる。

【００２１】本発明のポリスルホン系中空糸型血液浄化膜は、後述する乾湿式紡糸法により製膜される。紡糸直後の膜には、（ａ）ポリスルホン系ポリマー粒子間に存在し水洗や熱水洗の処理で容易に除去されるＰＶＰ、（ｂ）ポリスルホン系ポリマー粒子に弱く食い込んでいて水洗や熱水洗の処理では除去し難いが溶出可能なＰＶ

Ｐ、および（ｃ）ポリスルホン系ポリマー粒子に食い込んでいて抽出除去されないＰＶＰが存在していると推定される。従来の技術では、（ａ）タイプのＰＶＰを洗浄除去できたとしても、（ｂ）タイプのＰＶＰの除去が十分でなく、このために使用中での膜からの不溶化していないＰＶＰが徐々に溶出してくると考えられる。本発明では、膜からのＰＶＰの溶出を減少させるため、（ｂ）タイプのＰＶＰをできるだけ洗浄除去する方法を提案する。

【００２２】本発明の洗浄除去の第１の方法は、製膜したポリスルホン系中空糸膜をポリスルホン系ポリマーの良溶媒と貧溶媒の混合溶媒で洗浄する方法である。当然のこととして、この混合溶剤は、ポリスルホン系ポリマーを溶解させない範囲に、その混合比が設定されたものであり、かつ、不溶化していないＰＶＰを溶解させるものである。このような混合溶媒では、ポリスルホン系ポリマー粒子に膨潤作用を引き起こし、膜表層のポリスルホン系ポリマーを軟化させ、ＰＶＰの流動拡散性を向上すること等により、ポリスルホン系ポリマー粒子および緻密層内部からＰＶＰを引き抜くことで膜内を清浄化でき、その結果、溶出を高度に低減できるものと考えられる。

【００２３】第１の方法で用いられるポリスルホン系ポリマーの良溶媒としては、ジメチルアセトアミド（以下、ＤＭＡＣという）、Ｎ－メチル－２－ピロリドン、ジメチルスルホキシド（以下、ＤＭＳＯという）、ジメチルホルムアミド等が例示でき、単独または混合して用いられる。中でもＤＭＡＣ、および／またはＤＭＳＯが好ましく用いられる。また、ポリスルホン系ポリマーの貧溶媒としては、水、イソプロピルアルコール、エタノール、プロピルプロピレングリコール、テトラエチレングリコール等が例示できるが、中でも水が好ましく用いられる。このポリスルホン系ポリマーの良溶媒と貧溶媒の混合比は、溶媒の種類あるいは処理温度により条件が異なってくるため一概には決められないが、ポリスルホン系ポリマーの良溶媒を３０～９５重量％として使用するのが好ましい。例えば、３０～６０重量％のＤＭＡＣ水溶液、３０～６０重量％のＮ－メチルピロリドン水溶液、５０～９５重量％のＤＭＳＯ水溶液などが用いられる。また、ポリスルホン系ポリマーの良溶媒やポリスルホン系ポリマーの貧溶媒は単独で使用する必要はなく、２種あるいはそれ以上の良溶媒や貧溶媒のそれぞれ混合物の混合溶液でもかまわない。処理温度は、任意の温度でかまわないが、ポリスルホン系ポリマーの良溶媒の水溶液を用いる場合には、水の沸点以下が操作上望まれ、１０～９８℃が好ましい範囲であり、３０～９８℃がさらに好ましく、５０～９５℃が望ましい。

【００２４】本発明の洗浄除去の第２の方法は、製膜したポリスルホン系中空糸膜を高温のアルコール系溶剤で洗浄する方法である。膜を構成するポリスルホン系ポリマー粒子が膨潤し、弱く組み込まれたＰＶＰが遊離しやすくなるとともに、ＰＶＰの拡散速度が大きくなる。このために、水洗や熱水洗の処理では除去し難いＰＶＰが洗浄除去されると推定される。したがって、処理温度が低いと洗浄除去が不十分となり、高い方が望まれるが、高すぎると膜構造の変化が起こって膜性能が変動する。このため、本発明では１３０～１６０℃での洗浄処理が望まれる。好ましくは１３５～１５５℃であり、さらに好ましくは１４０～１５０℃である。

【００２５】本発明で使用できるアルコール系溶剤は、ＰＶＰの良溶媒であって、ポリスルホン系ポリマーに対して膨潤作用を有するものすべてがあげられるが、操作および装置の簡便性から、１３０℃以上の沸点あるいは分解点を有するアルコール系溶剤が好ましい。中でもグリセリンが好ましく用いられる。アルコール系溶剤の水分率は、少ない方が好ましく、５％以下が推奨でき、１％以下が好ましく、０．５％以下がさらに好ましい。第１の方法と第２の方法ともに、製膜したポリスルホン系中空糸膜として、あらかじめ水洗または熱水洗の工程を通して、除去されやすいＰＶＰと紡糸原液の溶媒を除去したものを用いる必要はない。紡糸原液の溶媒が残留していても、膜が膨張した状態にある方が、ＰＶＰの洗浄除去には効果的であることも推測される。

【００２６】また、第１の方法と第２の方法ともに、処理方法として下記の方法が例示できる。（１）洗浄液を浸漬させた状態で該膜を任意の温度に加熱させる。
（２）設定温度に調整した洗浄液に膜を浸漬させる。
（３）設定温度に調整した洗浄液を膜にシャワーする。
（４）設定温度に調整した洗浄液中に膜を走行させる。
いずれの方法でも可能であり、要は製膜したポリスルホン系中空糸膜が設定温度に調整された洗浄液に十分接触すればよい。処理時間は、処理方法によって異なり、バッチ操作となる（１）～（３）の方法では、１０分以上が好ましく、３０分以上がさらに好ましい。また、連続操作となる（４）においては、滞留時間が１５秒以上であることが必要で、２０秒以上がさらに好ましい。当然のこととして、処理後に用いられた溶剤を水洗および／または熱水洗等によって洗浄除去することが好ましい。

【００２７】本発明のポリスルホン系中空糸型血液浄化膜の内表面を走査型電子顕微鏡で観察すると、繊維状のポリスルホン系ポリマー（フィブリル）が中空糸繊維軸方向に並んで集合している構造を形成しており、フィブリル間に所々間隙がある。後述するように、製膜の条件によって、このフィブリル間が引き裂かれてその間隙が大きくなる。このような内表面を有する中空糸膜では、表面の平滑性が失われて血液適合性が悪くなるとともに、溶質分子の除去性にも悪く影響を与える。このため、本発明の中空糸膜では、中空糸膜内表面に０．８μｍ以上の引き裂かれた間隙を有さないことが望まれる。

【００２８】溶質分子のふるい分けは、溶質分子の大き

さと膜の孔の大きさによって決められる。すなわち、膜の孔径よりも小さい溶質分子は、膜を透過できるが、膜の孔径よりも大きな溶質分子は透過できない。この原理によって、溶質分子のふるい分けが起きるわけであるが、膜構造が不均一な膜の場合、膜断面方向で孔径が小さくなったところ、すなわち、本発明でいう選択分離層でふるい分けが起こる。一般に、ポリマー部分の緻密な構造のところで膜孔径は小さく、したがって、本発明でいう選択分離層は、膜断面の透過型電子顕微鏡像から判読できる。すなわち、膜断面の透過型電子顕微鏡の像を一定の幅で区切り、画像解析を行い、ポリマー部分が占める割合（組織率）を求める。この操作を中空糸膜内側から中空糸膜外側に向けて行うと、中空糸膜断面方向での組織率の分布が判明する。後述するように、膜内には孔径分布があるが、それを考慮し、本発明では、選択分離層を画像解析の幅を０．５～１．０μｍとして画像解析したとき、組織率の最も高かった値から、３０％以内の範囲にある部分と定義し、その厚みを測定した。

【００２９】膜の分画特性は多層構造モデルで説明される。すなわち、膜面に対して平行に（したがって、膜断面に対して垂直に）膜をスライスした多数の層が積層した構造を想定する。溶質分子は、この層毎にふるい分けられ、膜全体では多段濾過が行われていると考える。層毎に平均孔径は異なっているが、一つの層を取り上げると、その層内の孔径には分布があるため、平均孔径が最小の層だけが溶質のふるい分ける効果があるのではなく、平均孔径が若干大きくなった層も、通り抜けてきた大きな溶質分子を捕捉することができる。言い換えると、平均孔径が小さな層で孔径の大きなところをすり抜けてきた溶質分子が、平均孔径がやや大きくなったが溶質分子よりもサイズの小さな孔で十分に捕捉される。したがって、選択分離層としては、平均孔径が最小な層から若干大きくなった層までが有効である。

【００３０】分画特性のシャープさには、選択分離層の厚みが重要である。選択分離層が薄い場合は、平均孔径を少し上げて除去物質の透過性を良くしようとすると、有用な血漿蛋白であるアルブミンが透過しやすくなる。選択分離層内には孔径の分布があり、平均孔径をあげると、それに応じてアルブミンが透過できる孔も多くなるためと推測される。選択分離層が薄い場合は、一旦孔径の大きな部分からリークしたアルブミンを捕捉する別な選択分離層がないため、そのまま膜を透過することになる。また、紡糸条件の僅かな変動等の影響で選択分離層に構造欠陥が生じた場合にも、特に高分子量物質のリークが顕著になる。一方、選択分離層が厚い場合は、膜構造を比較的ルーズにしても、その厚さが厚ければアルブミンのリークは少なく、すなわち、分子量分画特性がシャープになる。これは、膜の選択分離層が厚いために、一つの層でアルブミンが透過しても、選択分離層のどこかの層で捕捉され、結果的に膜を透過する確率が低くなるためである。しかし、選択分離層が厚すぎると透過抵抗が大きくなりすぎるため、本発明では、２μｍ～１５μｍであることが必要であり、さらに好ましくは３μｍ～１２μｍであり、５μｍ～１０μｍがより望ましい。

【００３１】選択分離層の位置は、中空糸膜内側にあっても、断面中心部にあっても、あるいは中空糸膜内側と中空糸膜外側の両方にあっても、ふるい分け効果にはいずれでもよいが、一般に、中空糸膜内側に血液が流されるので、膜内孔の詰まりの原因となる血液中の蛋白の膜への浸入を防止するため、本発明では、選択分離層が中空糸膜内側にあることが好ましい。

【００３２】本発明におけるポリスルホン系中空糸型血液浄化膜の製膜に際しては、従来より一般的に知られている技術である乾湿式製膜技術を利用できる。すなわち、まずポリスルホン系ポリマーとＰＶＰを両方に共通溶媒に溶解し、均一な紡糸原液を調整する。このようなポリスルホン系ポリマーおよびＰＶＰを共に溶解する共通溶媒としては、例えば、ＤＭＡＣ、ＤＭＳＯ、Ｎ－メチル－２－ピロリドン、ジメチルホルムアミド、スルホラン、ジオキサン等の多種の溶媒あるいは上記２種以上の混合液からなる溶媒が挙げられる。また、孔径制御のため、紡糸原液には水などの添加物を加えてもよい。

【００３３】紡糸原液粘度が低すぎる場合、膜内部に大きなマクロボイドが顕著に現れるようになるが、血液浄化用の中空糸膜の場合、こうしたマクロボイドが多数存在すると血液透析中に血液凝固が起こりやすくなり、血液透析に用いる中空糸膜においては、マクロボイドがないことが好ましい。ここで言うマクロボイドとは、膜内でポリマーが存在しない空間のうち、その最大径が５μｍ以上のものを言う。一方、原液粘度が高くなりすぎると紡糸口金前の圧力が上がりすぎ、安定な紡糸ができなくなってくる。したがって、本発明では、紡糸原液粘度は１５００～６０００ｍＰａ・秒が必要であり、２０００～４０００ｍＰａ・秒の範囲が好ましい。本発明で言う粘度とは、製膜条件下の紡糸口金温度と同温度で紡糸原液を回転式の粘度計で測定したものである。

【００３４】紡糸原液の粘度は、ＰＶＰの分子量、紡糸原液中のポリスルホン系ポリマーおよびＰＶＰの濃度、紡糸原液の温度等に依存し、どの要因も膜構造の形成に重大な影響を及ぼす。本発明では、用いる原料を適切に選択し、濃度および温度の条件を設定することにより、上記の範囲に原液粘度を調整する。ポリスルホン系ポリマー系樹脂の添加量は、少なすぎると膜の形成が困難となり膜強度が弱くなりすぎてしまったり、多すぎると紡糸性が悪く孔径が小さくなりすぎる等の現象が生じてくるため、１５～２０重量%であることが好ましく、１６～１９重量%であることがさらに好ましい。しかし、この範囲であることが絶対ではなく、目的とする中空糸膜の性状によってはこの範囲より小さくすることも大きくすることもでき、他の紡糸条件を変化させることによっ

ても膜性状は変化するので、最適な組み合わせを適宜選択すればよい。

【００３５】ＰＶＰを紡糸原液へ添加する目的は、中空糸膜内にＰＶＰを残存させて膜に親水性を付与することである。したがって、用いるＰＶＰの分子量は重要である。すなわち、ＰＶＰの分子量が小さすぎると紡糸原液の凝固時、および得られた中空糸膜の洗浄時に、該ＰＶＰは容易に膜から溶出してしまうため、中空糸膜に親水性を付与するのに必要なＰＶＰを中空糸膜中に残存させるには、より多量のＰＶＰを紡糸原液へ添加することが必要となる。このため、ＰＶＰの中空糸膜への残存率を高めるには分子量が大きい方が好ましく、次式によって定義されるK-値が８８～９５、好ましくは８９～９４がよい。

【００３６】

【式１】

$$K\text{値} = \frac{\sqrt{300C\log Z + (C + 1.5C\log Z)^2} + 1.5C\log Z - C}{0.15C + 0.003C^2}$$

ここで、Ｚは濃度Ｃの溶液の相対粘度率、およびＣは（重量／容量）％の濃度である。

【００３７】紡糸原液中のポリスルホン系ポリマーとＰＶＰの相対量は、得られる中空糸膜の内表面ＰＶＰ濃度を決定するうえで極めて重要である。なぜなら、中空糸膜の内表面では中空内液と紡糸原液の接触により、急激な凝固がおこるため、その凝固面に存在するポリスルホン系ポリマーとＰＶＰの絶対量の比が、内表面にそのまま固定されるからである。紡糸原液中のポリスルホン系ポリマーに対するＰＶＰの重量比率が少なすぎる場合、表面ＰＶＰ濃度が上がらない。また、ポリスルホン系ポリマーに対してＰＶＰの重量比率が多すぎる場合、膜の強度が弱くなり、また、膜からのＰＶＰの溶出量が無視できなくなる。そこで、必要以上の強度を保ったまま、中空糸内表面のＰＶＰ濃度を３０％～４５％にしようとした場合、紡糸原液中のポリスルホン系ポリマーに対するＰＶＰの重量比率が、０．２５ないし０．５、好ましくは０．３ないし０．４８、さらに望ましくは０．３５ないし０．４５であることが必要である。

【００３８】中空内液は水、または水を主体とした凝固液が使用でき、目的とする中空糸膜の膜性能に応じて、その組成等は決めていけばよく、一概には決められないが、一般的には、紡糸原液に使った溶剤と水との混合溶液が好適に使用される。例えば、０～６０重量％のＤＭＡＣ水溶液などが用いられるが、特に０～４０重量％であることが好ましい。中空糸膜を製膜するに際してはチューブインオリフィス型の二重紡口を用い、該紡口から前記紡糸原液と該紡糸原液を凝固させるための中空内液とを同時に空中に押し出し、２０～８０ｃｍの空走部を走行させた後、紡口下部に設置した水を主体とする凝固浴中へ浸漬、凝固させた後巻き取る。

【００３９】本発明でいう紡糸ドラフト率とは、チューブインオリフィス型の二重紡口の環状スリット口金から、紡糸原液が吐出される時の吐出線速度と、中空糸膜の巻き取り速度の比であり、巻き取り速度を紡糸原液の吐出線速度で割った値である。低い紡糸ドラフト率の場合、紡糸口金のスリット幅をその分狭くする必要がある。血液浄化用の中空糸膜の場合、通常用いられる膜厚の範囲は２０～６０μｍである。このため、紡糸ドラフト率が低い場合、紡速を上げると原液の吐出線速度が増大し、紡糸口金での圧損が大きくなるため紡糸が不安定になりやすい。また、原液の吐出ムラが生じるため、膜構造が乱れ、透水性能、溶質透過性能のバラツキも大きくなる。さらに、スリット幅が狭いため、紡糸口金の芯合わせが困難になること、紡糸口金の作成自体が困難になり高コストになることなどの問題が指摘される。逆に、紡糸ドラフト率が高すぎると、すなわち、紡糸口金からの原液の吐出線速度に対して巻き取り速度が速すぎる場合、紡糸口金直下では、中空糸内表面が凝固しながら、強く引っ張られることにより、膜内表面の緻密層が引き裂かれたような形状となり、特別大きな孔径を有する孔が生成しやすくなるため、有用蛋白であるアルブミンのリーク問題が生じる。この問題は、紡糸原液の組成を変える、紡糸原液の温度を高くするなどの方法で原液粘度を低く抑えることで、ある程度は改善可能であるが十分でない。したがって、本発明では、紡糸ドラフト率は１．１～１．９が必要であり、１．１～１．５の範囲であることが好ましい。

【００４０】ここで言う原液の吐出線速度とは、紡糸時に紡糸口金から紡糸原液が吐出される時の線速度で、単位時間当たりの紡糸原液の吐出流量を紡糸口金の原液吐出断面積で割った値である。原液の吐出線速度が大きくなると、原液の吐出ムラが大きくなり、膜の構造ムラにより大きな孔径を有する孔が形成して、アルブミンのリークが生じてしまう。本発明では、原液の吐出線速度は９０ｍ／ｍｉｎ以下であることが必要であり、７０ｍ／ｍｉｎ以下であることが好ましく、さらには、６０ｍ／ｍｉｎ以下であることがより好ましい。

【００４１】選択分離層を制御するには、次に示すような製膜工程が重要である。まず、中空内液の種類および濃度が重要であり、中空内液中の溶剤濃度を高くすると、凝固力が弱くなるために緩やかに凝固が進む結果、緻密な凝集構造をとることができず、選択分離層は疎な構造になる。次に、紡糸原液の粘度が重要で、粘度が高いと凝固時にポリスルホン系ポリマーの移動が抑えられ、同条件下で粘度が低い場合に比べて選択分離層は厚くなる。紡糸原液の粘度は、親水性高分子の分子量、紡糸原液中のポリスルホン系ポリマーおよび親水性高分子

の濃度、紡糸原液の温度等に依存し、どの要因も選択分離層の形成に重大な影響を及ぼす。また、紡糸ドラフトも重要な要因で、厚い選択分離層を持たせるためには、紡糸ドラフト率を上げた方が良い。選択分離層の形成に影響を及ぼす因子は、この他にも、紡糸口金から凝固浴までの空走部の距離、紡糸口金サイズ、凝固浴の温度と組成、紡速、紡糸原液に使用する溶剤などがあるが、溶質の透過性能との兼ね合い、目的等を考慮して設定する必要がある。

【００４２】上記のようにして、紡糸され、巻き取られた中空糸膜は公知の方法で後処理される。すなわち、熱水等による洗浄で溶剤および過剰なＰＶＰが除去され、必要に応じてグリセリンを付与した後、乾熱乾燥される。また、中空糸膜を巻き取った後に後処理するのでなく、熱水等による洗浄や乾熱乾燥した後に巻き取る方法も本発明の範囲内であり、本発明で重要なことは、紡糸原液粘度を１５００～６０００ｍＰａ・秒に調整し、紡糸口金からの吐出線速度が９０ｍ／ｍｉｎ以下の条件で、紡糸ドラフト率を１．１～１．９以下にすることである。

【００４３】

【発明の実施の態様】以下に実施例および比較例を用いて本発明を詳細に説明するが、本発明は、これにより何ら限定されるものではない。本発明での透水量および篩い係数は、以下のように測定したものである。すなわち、乾燥させたポリスルホン系選択透過中空糸膜１００本からなるミニモジュール（有効長２５ｃｍ）を組立成型し、２００ｍｍＨｇの圧力条件のもとフロー法にて透水量をｍｌ／Ｈｒ／m^2／ｍｍＨｇの単位で測定した。続いてさらに、牛血漿を用いてβ_2－MG、アルブミンの篩い係数を測定した。糸強度はＯＲＩＥＮＴＥＣ社ＴＥＮＳＩＬＯＮ；ＲＴＣ－１２１０を用い、中空糸膜を破断するまで引っ張り、その時かかった最大荷重を強度とした。

【００４４】

【実施例１】ポリスルホン樹脂（アモコ・パフォーマンス・プロダクツ社製、Ｐ－１７００）１７重量部、ポリビニルピロリドン（ビー・エー・エス・エフ社製、Ｋ－９２）７重量部、ＤＭＡＣ７６重量部からなる均一な紡糸原液を作成した。この紡糸原液粘度は６５℃で３４００ｍＰａ・ｓであった。この紡糸原液を６５℃に保ったまま、１５％ＤＭＡＣの中空内液とともにスリット幅５９．５μｍの環状口金から吐出し、６０ｃｍ下方に設けた５５℃の水中に浸漬し、７０m/minの速度で巻き取った。乾燥時の中空糸膜厚を４５μｍに合わせるように紡糸原液の吐出量を調整したので、原液の吐出線速は４９．３ｍ／ｍｉｎとなり、ドラフト率は１．４２であった。得られた中空糸膜束をつり下げ、８５℃に加温した４０重量％のＤＭＡＣ水溶液を８０分シャワーした。その後、９０℃で熱水洗浄し、２０％グリセリン水溶液に浸漬してグリセリンを付着させた。次いで、７５℃にて１１時間熱風乾燥させた。続いて、中空糸膜を二亜硫酸ナトリウム６００ｐｐｍと炭酸ナトリウム３００ｐｐｍを溶解させた水溶液に浸漬させ、２５ｋＧｙのγ線を照射し、ポリスルホン系血液浄化膜を得た。得られた中空糸膜を四酸化オスミウム水溶液で染色し、脱水後、エポキシ樹脂で包埋し、硬化後、超ミクロトームを用いて約６０ｎｍの超薄切片を作成し、ＴＥＭ（ＪＥＭ２０００ＦＸ）観察を行った。得られたＴＥＭ像を用いて、０．７μｍ間隔で中空糸膜内表面側から外表面側に向けて画像解析装置（ＩＰ－１０００：旭化成社製）により組織率の測定を行った。測定結果および膜の評価結果を表１に示す。また、この膜の内表面の様子を図１に示す。引き裂かれた構造はなく、平滑な表面になっている。

【００４５】

【実施例２】中空糸膜の抽出洗浄を８０℃、４０％ＤＭＡＣ水溶液での８０分のシャワーの代わりに１３０℃のグリセリンを３時間シャワーした以外は、実施例１と同様にしてポリスルホン系血液浄化膜を得た。得られた結果を表１に示す。

【実施例３】８０℃、４０％ＤＭＡＣ水溶液での８０分のシャワーによる抽出洗浄を行わない以外は、実施例１と同様にしてポリスルホン系血液浄化膜を得た。得られた結果を表１に示す。

【００４６】

【実施例４】ポリスルホン樹脂（アモコ・パフォーマンス・プロダクツ社製、Ｐ－１７００）１７重量部、ポリビニルピロリドン（ビー・エー・エス・エフ社製、Ｋ－８９）７重量部、ＤＭＡＣ７６重量部からなる均一な紡糸原液を作成した。この紡糸原液粘度は８０℃で１６５０ｍＰａ・ｓであった。この紡糸原液を８０℃に保ったまま、１５％ＤＭＡＣの中空内液とともにスリット幅５９．５μｍの環状口金から吐出し、６０ｃｍ下方に設けた５５℃の水中に浸漬し、７０ｍ／ｍｉｎで巻き取った。その後は、実施例１と同様にしてポリスルホン系血液浄化膜を得た。得られた結果を表１に示す。

【００４７】

【実施例５】ポリスルホン樹脂（アモコ・パフォーマンス・プロダクツ社製、Ｐ－１７００）１６重量部、ポリビニルピロリドン（ビー・エー・エス・エフ社製、Ｋ－８９）７．８重量部、ＤＭＡＣ７６．２重量部からなる均一な紡糸原液を作成した。この紡糸原液粘度は７０℃で２５００ｍＰａ・ｓであった。この紡糸原液を７０℃に保ったまま、１５％ＤＭＡＣの中空内液とともにスリット幅５９．５μｍの環状口金から吐出し、６０ｃｍ下方に設けた５５℃の水中に浸漬し、７０ｍ／ｍｉｎで巻き取った。その後は、実施例１と同様にしてポリスルホン系血液浄化膜を得た。得られた結果を表１に示す。

【００４８】

【実施例６】ポリスルホン樹脂（アモコ・パフォーマン

ス・プロダクツ社製、Ｐ－１７００）１７重量部、ポリビニルピロリドン（ビー・エー・エス・エフ社製、Ｋ－９２）５．５重量部、ＤＭＡＣ７８．５重量部からなる均一な紡糸原液を作成した。この紡糸原液粘度は５０℃で２４００ｍＰａ・ｓであった。この紡糸原液を５０℃に保ったまま、１５％ＤＭＡＣの中空内液とともにスリット幅５９．５μｍの環状口金から吐出し、６０ｃｍ下方に設けた５５℃の水中に浸漬し、７０ｍ／ｍｉｎで巻き取った。その後は、実施例１と同様にしてポリスルホン系血液浄化膜を得た。得られた結果を表１に示す。

【００４９】

【実施例７】ポリスルホン樹脂（アモコ・パフォーマンス・プロダクツ社製、Ｐ－１７００）１７重量部、ポリビニルピロリドン（ビー・エー・エス・エフ社製、Ｋ－８９）６．３重量部、ＤＭＡＣ７６．７重量部からなる均一な紡糸原液を作成した。この紡糸原液粘度は５５℃で２８２０ｍＰａ・ｓであった。この紡糸原液を５５℃に保ったまま、１５％ＤＭＡＣの中空内液とともにスリット幅５９．５μｍの環状口金から吐出し、６０ｃｍ下方に設けた５５℃の水中に浸漬し、７０ｍ／ｍｉｎで巻き取った。その後は、実施例１と同様にしてポリスルホン系血液浄化膜を得た。得られた結果を表１に示す。

【００５０】

【比較例１】γ線を照射しない以外は、実施例６と同様にしてポリスルホン系血液透析膜を得た。得られた結果を表１に示す。

【比較例２】中空糸膜を二亜硫酸ナトリウム６００ｐｐｍと炭酸ナトリウム３００ｐｐｍを溶解させた水溶液に浸漬させる代わりに水中に浸漬し、５０ｋＧｙのγ線を照射した以外は、実施例６と同様にしてポリスルホン系血液透析膜を得た。得られた結果を表１に示す。

【００５１】

【比較例３】紡糸原液を１５％の中空内液とともにスリット幅５９．５μｍの環状口金から吐出する代わりに、スリット幅１２５μｍの環状口金から吐出させた以外は、実施例１と同様にしてポリスルホン系血液浄化膜を得た。得られた結果を表１に示す。また、この時ドラフト率は３．２であった。この膜の内表面は、ドラフトの影響で大きく引き裂かれた構造になっており、その様子を図２に示す。

【比較例４】紡糸原液を１５％ＤＭＡＣの中空内液とともにスリット幅５９．５μｍの環状口金から吐出する代わりに、スリット幅５０μｍの環状口金から吐出させた以外は、実施例１と同様にしてポリスルホン系血液浄化膜を得た。得られた結果を表１に示す。また、この時ドラフト率は１．０であった。この膜の内表面はドラフトが低いため、引き裂かれたような構造はないが、原液の吐出ムラと思われる影響で、構造ムラが見られる。その様子を図３に示す。

【００５２】

【比較例５】ポリスルホン樹脂（アモコ・パフォーマンス・プロダクツ社製、Ｐ－１７００）１７重量部、ポリビニルピロリドン（ビー・エー・エス・エフ社製、Ｋ－９２）３．５重量部、ＤＭＡＣ７９．５重量部からなる均一な紡糸原液を作成した。この紡糸原液粘度は５０℃で１２５０ｍＰａ・ｓであった。この紡糸原液を５０℃に保ったまま、１５％ＤＭＡＣの中空内液とともにスリット幅５９．５μｍの環状口金から吐出し、６０ｃｍ下方に設けた５５℃の水中に浸漬し、７０ｍ／ｍｉｎで巻き取った。その後は、実施例１と同様にしてポリスルホン系血液浄化膜を得た。得られた結果を表１に示す。

【００５３】

【表１】

表1

	バルクPVP (%)	ESCA:PVP (%)	溶出PVP (mg/m2)	Alb SC (%)	β2−Mg (%)	透水 (＊)	残血	緻密層 (μm)	引き裂き	強度 (g/hf)	可溶性PVP (mg/g-HF)
実施例1	7.0	38	0.25	0.003	0.64	210	○	10.5	無し	17.1	8.0
実施例2	7.1	38	0.26	0.003	0.64	205	○	10.6	〃	17.2	8.3
実施例3	8.9	39	1.01	0.002	0.55	175	○	11.2	〃	17.1	11.9
実施例4	5.0	35	0.27	0.004	0.68	287	○	4.8	〃	19.2	6.9
実施例5	8.1	44	0.25	0.004	0.61	165	○	8.2	〃	16.3	9.6
実施例6	4.5	30	0.41	0.005	0.70	514	○	9.2	〃	19.8	7.8
実施例7	5.5	33	0.30	0.002	0.68	222	○	7.5	〃	19.0	7.8
比較例1	4.8	31	2.20	0.003	0.63	229	○	9.5	〃	19.8	43.0
比較例2	4.8	31	0.10	0.003	0.67	209	×	9.5	〃	19.8	0.2
比較例3	4.6	32	0.25	0.010	0.69	255	×	9.3	有り	19.8	8.0
比較例4	7.3	38	0.28	0.009	0.68	245	○	9.2	ムラ	17.0	8.1
比較例5	3.2	24	0.95	0.011	0.85	702	×	6.8	〃	21.2	2.0

(＊)ml／Hr／m2／mmHg

【００５４】実施例１～７および比較例１～５の中空糸膜について、残血評価を実施した。すなわち、１６ｃｍ長の中空糸膜１２０本をモジュールに組み、生理食塩水２０ｍｌで洗浄した。その後、犬頸動脈からペリスタポンプを介して取り出した血液を２ｍｌ／分の流量で、中空糸内側に１０分流した。生理食塩水５ｍｌで血液を押し出した後、モジュールを解体し、残血の度合いを評価した。その結果、比較例２、３、５、の中空糸では、残

血が認められたが、その他の比較例および実施例の中空糸膜では、残血はほとんどないか少量にとどまっていた。

【００５５】

【発明の効果】以上述べたように、本発明のポリスルホン系血液浄化膜は、血液適合性を改良し、血液側へのポリビニルピロリドンの溶出量が極めて少なく、さらに、分子量分画性の優れた中空糸膜である。この発明により、これからの透析治療において非常に有意義な人工腎臓を提供することができる。

【図面の簡単な説明】

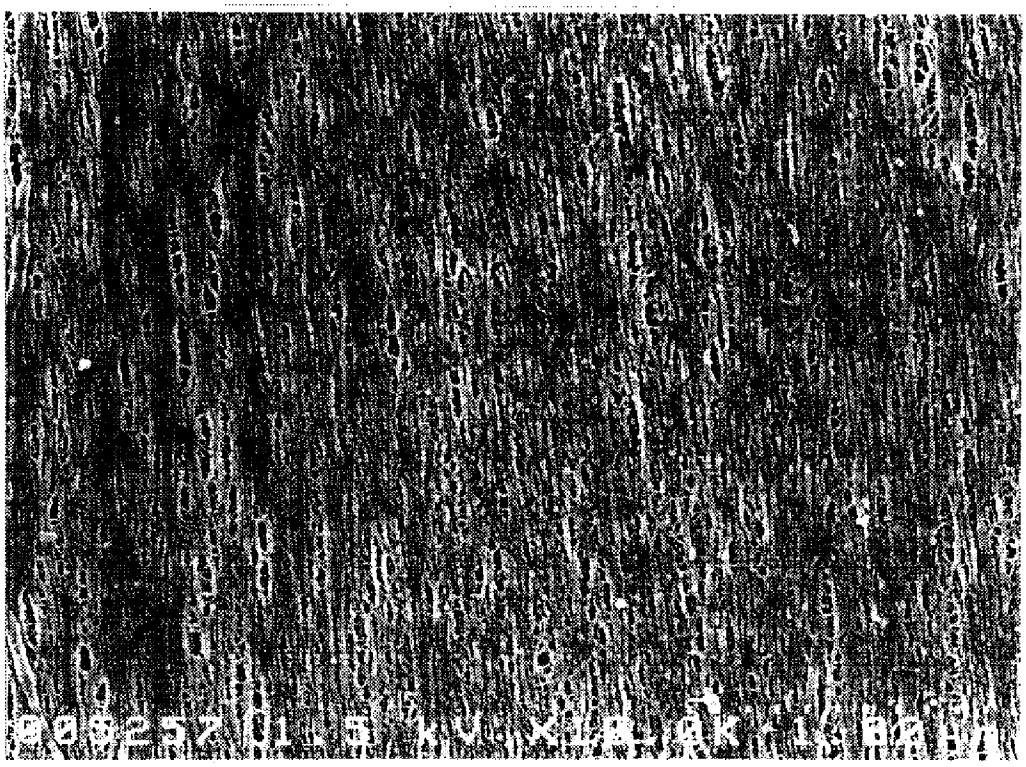
【図１】実施例１の中空糸膜の内表面を走査型電子顕微鏡により観察した像である（上段：１００００倍、下段：３００００倍）。内表面は平滑で、フィブリルが中空糸繊維軸方向に並んで集合しているのが観察される。

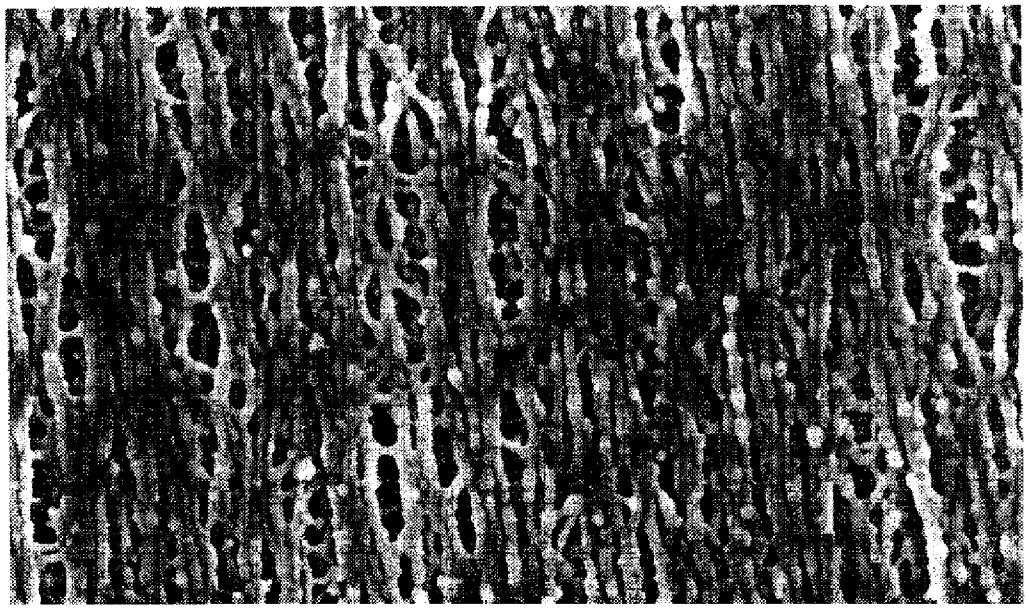
【図２】比較例３の中空糸膜の内表面を走査型電子顕微鏡により観察した像である（上段：１００００倍、下段：３００００倍）。内表面に２μｍ程度の引き裂かれたような間隙がある。

【図３】比較例４の中空糸膜の内表面を走査型電子顕微鏡により、１０００倍の倍率で観察した像である。原液の吐出ムラと思われる影響で構造ムラが見られる。フィブリル間が粗くなっている部分をａ、密となっている部分をｂとして、それぞれ１５０００倍に拡大した像を中段、下段に示す。

【図１】

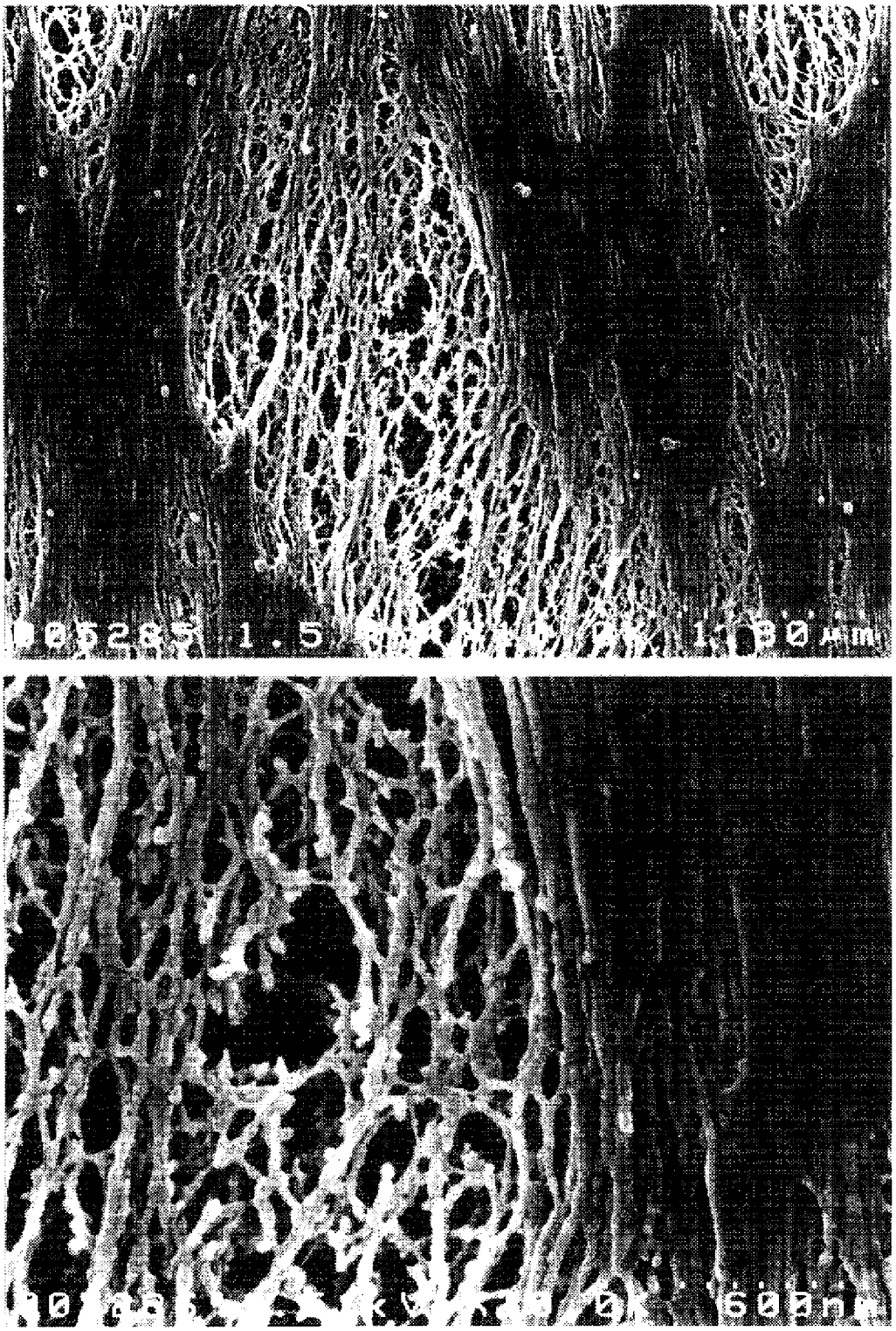
図面代用写真



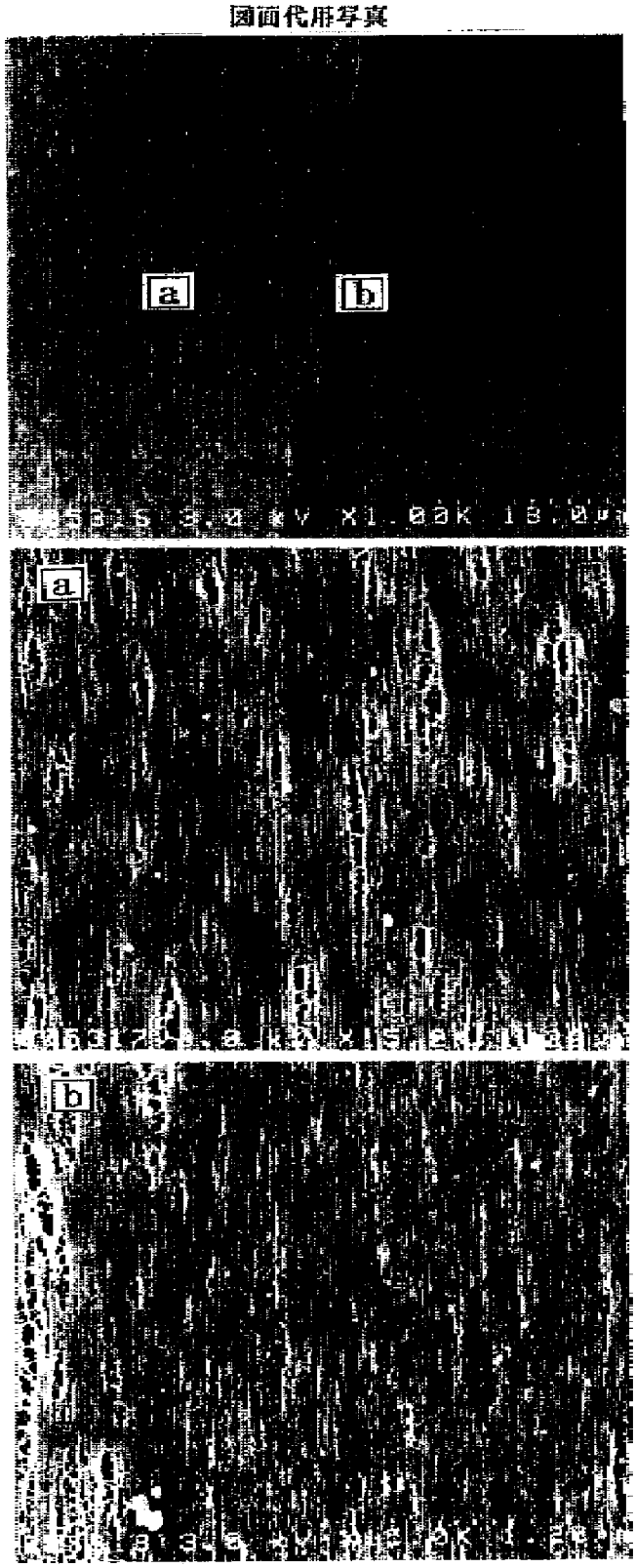


【図２】

図面代用写真



【図３】



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(54) POLYSULFONE HOLLOW FIBER TYPE BLOOD PURIFYING MEMBRANE AND ITS PRODUCTION

(57)Abstract:
PROBLEM TO BE SOLVED: To prepare a polysulfone blood purifying membrane improved in biocompalibility, extremely reduced in the elution of polyvinyl pyrrolidone on the inner surface side of hollow fiber and improve in separation characteristics.
SOLUTION: In a polysulfone hollow fiber type blood purifying membrane, a selective separation layer having separation function substantially is present on the inner surface side of each hollow fiber membrane and contains 1-10 wt.% of polyvinyl pyrrolidone wherein 5-50% thereof is soluble in water and the concn. thereof of an inner surface is 30-45%. This polysulfone hollow fiber type blood purifying membrane is a hollow fiber membrane improved in blood compatibility, extremely reduced in the elution of polyvinyl pyrrolidone to a blood side and excellent in mol.wt. fractionality. By this constitution, an artificial kidney extremly significant in future dialytic treatment can be provided.

LEGAL STATUS

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[Date of registration]

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[Date of extinction of right]

CLAIMS

[Claim(s)]
[Claim 1] Polysulfone system hollow filament mold blood purification film which the polyvinyl pyrrolidone contains one to 10% of the weight, and this 5 - 50% of polyvinyl pyrrolidone is fusibility at water in the polysulfone system hollow filament mold blood purification film which the selection detached core which has isolation substantially exists in a hollow fiber internal-surface side, and contains a polyvinyl pyrrolidone, and is characterized by the concentration of the polyvinyl pyrrolidone in a hollow fiber internal surface being in 30 to 45% of range.
[Claim 2] Polysulfone system hollow filament mold blood purification film according to claim 1 whose concentration of the polyvinyl pyrrolidone in a hollow filament internal surface is 33% to 40%.
[Claim 3] The elution volume of the polyvinyl pyrrolidone when carrying out the circulation extract of the hollow fiber inside in an alcoholic water solution 40% is 2 1m of film surface products. Polysulfone system hollow filament mold blood purification film according to claim 1 characterized by being 0.5mg or less of hits.
[Claim 4] Polysulfone system hollow filament mold blood purification film according to claim 1 characterized by not having the torn gap 0.8 micrometers or more in a hollow fiber internal surface.
[Claim 5] Polysulfone system hollow filament mold blood purification film according to claim 1 characterized by the thickness of a selection detached core being 2-15 micrometers.
[Claim 6] The manufacture approach of the polysulfone system hollow filament mold blood purification film characterized by making a part of polyvinyl pyrrolidone in this hollow fiber insolubilize by the physicochemical approach after it contains a polysulfone system polymer 15 to 20% of the weight and the weight ratio of the polyvinyl pyrrolidone to a polysulfone system polymer carries out spinning of the hollow fiber using the polymer solution which are 0.25-0.5.
[Claim 7] The manufacture approach of the polysulfone system hollow filament mold blood purification film according to claim 6 characterized by irradiating a radiation and making a part of polyvinyl pyrrolidone insolubilize after making the hollow fiber behind spinning into the damp or wet condition more than percentage of saturatel water content.
[Claim 8] The manufacture approach of the polysulfone system hollow filament mold blood purification film according to claim 6 characterized by extracting and washing a polyvinyl pyrrolidone with the solvent or alcohols solvent which is a partially aromatic solvent of the good solvent and poor solvent of a polysulfone system polymer about the hollow fiber behind spinning, and dissolves a polyvinyl pyrrolidone.
[Claim 9] The manufacture approach of the polysulfone system hollow filament mold blood purification film according to claim 8 characterized by for the good solvent of a polysulfone system polymer being dimethylacetamide or/and dimethyl sulfoxide, and the poor solvent of a

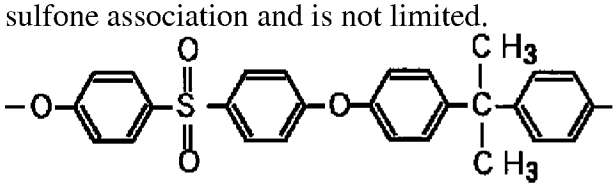
polysulfone system polymer being water.
[Claim 10] The manufacture approach of the polysulfone system hollow filament mold blood purification film according to claim 6 characterized by carrying out extract washing of the hollow fiber behind spinning with a 130-160-degree C alcohols solvent.
[Claim 11] The manufacture approach of the polysulfone system hollow filament mold blood purification film according to claim 10 characterized by an alcohols solvent being a glycerol.
[Claim 12] The manufacture approach of the polysulfone system hollow filament mold blood purification film according to claim 6 that viscosity which dissolved the polysulfone system polymer and the polyvinyl pyrrolidone in these common solvents is characterized by carrying out spinning of the spinning undiluted solution of 1500 - 6000mPa and a second with the rates 1.1-1.9 of a draft, and 90 or less m/min of regurgitation linear velocity.

DETAILED DESCRIPTION

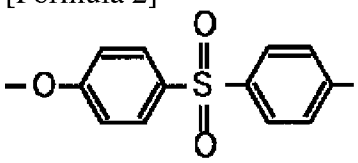
[Detailed Description of the Invention]
[0001]
[Field of the Invention] This invention relates to the polysulfone system hollow filament mold blood purification film and its manufacture approach. In detail, it is related with the polysulfone system blood purification film with which haemocompatibility and a separation property were improved, and its manufacture approach.
[0002]
[Description of the Prior Art] In recent years, the ultrafiltration method which is the separation technology using a permselectivity demarcation membrane, reverse osmosis, a gas separation method, etc. are put in practical use in various kinds of fields, and the demarcation membrane made from the raw material which fits the various applications respectively is marketed. As a raw material of a permselectivity demarcation membrane, polymers, such as a cellulose type, a cellulose acetate system, a polyamide system, a polyacrylonitrile system, a polyvinyl alcohol system, a polymethylmethacrylate system, a polysulfone system, and a polyolefine system, are used. Since physicochemical qualities, such as thermal resistance, acid resistance, alkali resistance, and oxidation resistance, are excellent especially, the polysulfone system polymer attracts attention also especially as medical application in recent years and an industrial use demarcation membrane raw material.
[0003] However, since a polysulfone system polymer is a hydrophobic raw material, the permselectivity demarcation membrane made from this does not have good water wettability compared with the permselectivity demarcation membrane made from the hydrophilic polymer. For this reason, when it considers as medical application, adsorption of a plasma protein tends to take place, and since the omission of air bubbles is bad, the fault of resulting in blood coagulation because the air bubbles which remained into the film activate ejection and a platelet into blood is pointed out.
[0004] Then, the examination for giving a hydrophilic property to the permselectivity demarcation membrane which consists of a polysulfone system polymer, and raising water wettability is made, and the permselectivity demarcation membrane which made the polysulfone system polymer contain a hydrophilic polymer, and its process are proposed as the one approach. However, if there are few contents of a hydrophilic polymer, water wettability will worsen, blood coagulation is caused, and when objection has many contents of a hydrophilic polymer,

there is a trouble that the elution volume of the hydrophilic polymer from the film after film production increases.
[0005] JP,61-238306,A and 63-97666 -- a polysulfone system polymer, a hydrophilic polymer, and this polysulfone system polymer -- receiving -- a non-solvent -- or -- a swelling agent -- although the manufacture approach of the polysulfone system demarcation membrane using the system which added the additive as a film production undiluted solution is indicated, there is no publication of the approach of reducing elution of a hydrophilic polymer. Moreover, by performing radiation treatment and/or heat treatment for the polysulfone system demarcation membrane manufactured by the above-mentioned approach to JP,63-97205,A, 63-97634, and JP,4-300636,A, a hydrophilic polymer is insolubilized and the method of reducing elution of a hydrophilic polymer is indicated. However, probably because a hydrophilic polymer insolubilizes according to this bridge formation, haemocompatibility worsens.
[0006] In JP,6-165926,A, processing with the solution which has a poor solvent operation for the polysulfone system hollow fiber containing polyglycols and a vinyl-pyrrolidone system polymer to rinsing, heat rinsing processing, and this polysulfone system polymer is performed, and the method of manufacturing the hollow fiber film is indicated. However, processing with the solvent which has this poor solvent operation is performed at 90 degrees C, and extract clearance is not enough.
[0007] It is related with a spinning draft. To JP,5-54373,B A hydrophobic polymer, Carried out spinning of the undiluted solution of hypoviscosity which consists of hydrophilic polymers and those common solvents, and were manufactured. The process of the hollow fiber for blood processing which contains a hydrophilic polymer one to 10% of the weight, and has 3 - 10% of water absorption capacity is indicated. In this It is, when the thing with same rate which comes out of the spinneret of a spinning constituent and generated taking over rate of fiber, i.e., the rate of a spinning draft is 1, is desirable. However, when the rate of a draft is 1 actually, it is difficult to raise spinning speed. If the discharge quantity of an undiluted solution is raised in order to raise spinning speed, the regurgitation linear velocity of that the pressure loss of a spinneret becomes large and a spinning undiluted solution will increase, and problems, like that become easy to produce the regurgitation unevenness of a spinning undiluted solution, and spinning becomes instability and membrane structure is confused will arise. Moreover, although it is that a nozzle draft is usually set as the range of 2-5 in JP,6-165926,A since structure will become instability if a nozzle draft is enlarged extremely or it is made small, if the rate of a draft exceeds 2, it will become the structure where the hollow filament internal surface was torn, and troubles, such as becoming easy to leak the albumin which is useful protein, are pointed out.
[0008] In recent years, as a cause of dialysis complication, low-molecular proteins, such as beta2-microglobulin (beta2-MG), are mentioned, and highly efficient permeable membrane which can remove these from blood efficiently is desired. In the above-mentioned Prior art, sufficient examination to fractionation nature is not made and it is not necessarily a satisfaction **** thing. That is, it is because leak of useful proteins, such as albumin, will pose a problem if the membranous transparency engine performance is improved in order to improve clearance of low-molecular protein.
[0009]
[Problem(s) to be Solved by the Invention] This invention cancels the trouble of the conventional technique, improves haemocompatibility, and there is very little elution of the polyvinyl pyrrolidone by the side of the internal surface of a hollow fiber, and, moreover, it aims at offering the polysulfone system blood purification film which improved the membranous

separation property, and its manufacture approach.
[0010]
[Means for Solving the Problem] As a result of inquiring wholeheartedly that this invention persons should attain the above-mentioned technical problem, in the hollow filament-like polysulfone system hollow filament mold blood purification film containing a polyvinyl pyrrolidone (henceforth PVP), by making a part of PVP into a condition insoluble in water, and making suitable PVP concentration of a hollow fiber internal surface, there was little elution of PVP from an internal surface, it was excellent in haemocompatibility, and found out that a pure hollow fiber could moreover be offered. Moreover, by extracting PVP with a suitable solvent, the hollow fiber was washed and elution of PVP from an internal surface found out still fewer things for which a pure hollow fiber can be offered. Furthermore, while the thickness with the effectiveness which screens a solute molecule from the spinning undiluted solution which has suitable viscosity substantially in the film by carrying out spinning at the suitable rate of a spinning draft of a selection detached core was appropriately controllable, it tears to a hollow fiber internal surface, there is no structure, and it found out that the sharp polysulfone system blood purification film of the fractionation nature which can perform clearance of an undesired substance and recovery of the useful matter efficiently could be offered.
[0011] That is, in the polysulfone system hollow filament mold blood purification film which the selection detached core in which this invention has isolation substantially exists in a hollow fiber internal-surface side, and contains a polyvinyl pyrrolidone, it contains 10% of the weight, and 5 of this polyvinyl pyrrolidone thru/or 50% are fusibility at water, and a polyvinyl pyrrolidone is the polysulfone system blood purification film characterized by 1 thru/or the concentration of the polyvinyl pyrrolidone of an internal surface being in 30 to 45% of range.
[0012] After this invention contains a polysulfone system polymer 15 to 20% of the weight again and the weight ratio of the polyvinyl pyrrolidone to a polysulfone system polymer carries out spinning of the hollow fiber using the polymer solution which are 0.25-0.5, it is the manufacture approach of the polysulfone system hollow filament mold blood purification film characterized by making a part of polyvinyl pyrrolidone in this hollow fiber insolubilize by the physicochemical approach.
[0013] The manufacture approach of the polysulfone system blood purification film characterized by this invention extracting and washing a polyvinyl pyrrolidone with the solvent or alcohols solvent which is a partially aromatic solvent of the good solvent and poor solvent of a polysulfone system polymer about the hollow fiber behind spinning, and dissolves a polyvinyl pyrrolidone further, The viscosity which dissolved the polysulfone system polymer and the polyvinyl pyrrolidone in these common solvents and the spinning undiluted solution of 1500 - 6000mPa and a second It is the manufacture approach of the polysulfone system hollow filament mold blood purification film characterized by carrying out spinning with the rates 1.1-1.9 of a draft, and 90 or less m/min of regurgitation linear velocity. This invention is explained below at a detail.
[0014] The polysulfone system polymer said by this invention is [Formula 1] when an example is given, although it is especially the generic name of the macromolecule connective which has sulfone association and is not limited.



[Formula 2]



It is marketed widely, and since acquisition is also easy, the polysulfone system polymer resin which is alike and has the repeat unit shown is used preferably. It is the brand name of "YUDERU" from the Amoco performance products company, and from BASF, it is marketed by the brand name of an "ultra zone", and, as for the polysulfone resin with the former structure, some classes exist with polymerization degree etc.

[0015] Moreover, PVP of this invention is the water-soluble high molecular compound to which vinyl polymerization of the N-vinyl pyrrolidone was carried out, and is the brand name of a "plus boss" in insertion sequence Py, and is marketed by the brand name of "Kollidon" from BASF, and has the polyvinyl pyrrolidone of some molecular weight, respectively. If the PVP content in a hollow fiber is low, since the PVP concentration of the hollow fiber internal surface in contact with blood will not go up but a membranous hydrophilic property will worsen, blood coagulation becomes easy to happen when blood is contacted. Moreover, although what is necessary is just to make high PVP concentration in the polymer solution used for spinning in order to enlarge the PVP content in a hollow fiber so that it may mention later, the viscosity of a polymer solution also goes up and spinning becomes impossible. For this reason, in this invention, PVP is contained in a hollow fiber in 1 - 10% of the weight of the range in a hollow fiber. It is 2.5 - 8% of the weight of the range preferably.

[0016] The PVP content in a hollow fiber is easily computable with the elemental-analysis value of nitrogen and sulfur. Moreover, thermal cracking gas chromatography can analyze a hollow fiber, and it can ask easily also by analyzing the peak of the PVP origin. PVP is a polymer which is easy to melt into water, and is easily eluted into water or blood from a hollow fiber. Although the elution from a hollow fiber will be thoroughly lost if all PVP to contain is insolubilized, the hydrophilization effectiveness on the front face of the film also becomes weak. For this reason, they are 5 of the whole quantity which is made to insolubilize a part of PVP according to bridge formation, and contains PVP of fusibility in water in this invention at a hollow fiber thru/or 50%. If it is in this range, the elution from a hollow fiber will also be suppressed and the hydrophilization effectiveness on the front face of the film will also be maintained.

[0017] The amount of PVP of fusibility is the amount of PVP in the film which has not insolubilized according to bridge formation, and water is asked for it as follows. That is, a hollow fiber is thoroughly dissolved by the N-methyl-2-pyrrolidone. Subsequently, water is added in this polymer solution and a polysulfone system polymer is settled. The quantum of the amount of PVP in the digestive liquor obtained is carried out with liquid chromatography after standing. A factor important for the haemocompatibility of a hollow fiber is a hydrophilic property on the front face of the film, and the PVP concentration of a film internal surface is important for it in the polysulfone system hollow fiber containing PVP. When surface PVP concentration is too low, a film front face shows hydrophobicity, a plasma protein tends to adsorb, and the coagulation of blood also tends to take place. That is, haemocompatibility serves as a defect. Conversely, if surface PVP concentration is too high, the elution volume to the blood of PVP etc. will increase and the result which is not desirable will be given for the object and

application of this invention. Therefore, the concentration of the film internal surface PVP in this invention is 30% - 45% of range, and is 33% - 40% preferably.
[0018] The PVP concentration of a hollow fiber internal surface is determined by X-ray photoelectron spectroscopy (ESCA). That is, after measurement of ESCA of a hollow fiber internal surface arranges a sample in on a double-sided tape, a cutter cuts it open to fiber shaft orientations, and it puts in order what was extended so that the inside of a hollow fiber might become a table, is made into a sample, and is measured by the usual approach. That is, it asks for the surface concentration (A) of nitrogen, and sulphuric surface concentration (B) from the integrated intensity of N1s and an S2p spectrum C1s and O1s using the relative sensitivity coefficient of equipment attachment, and is surface PVP concentration =Ax100/(Ax111+Bx442). Surface PVP concentration is computed more.
[0019] Elution of PVP from a hollow fiber is estimated by this invention by the elution volume when carrying out the circulation extract of the hollow fiber inner surface in an ethanol water solution 40%. A hollow fiber is included in a module, and it circulates through an ethanol water solution at 37 degrees C 40% to a blood side for 4 hours, and, specifically, is evaluated by measuring the amount of PVP extracted. Although 37-degree C blood is suitable, since past [a minute amount] and the interfering substance have much eluted hydrophilic macromolecule as an extract medium, the quantum of PVP extracted is difficult. Moreover, as an extract medium, the extract force of water is weak and the quantum of PVP extracted is difficult. 40% ethanol water solution is suitable as an extract medium.
[0020] In this invention, a part of PVP is made to insolubilize according to bridge formation as mentioned above, and the elution from a hollow fiber is controlled. Furthermore, the elution volume of the polyvinyl pyrrolidone when elution of PVP from a hollow fiber being controlled and carrying out the circulation extract of the hollow fiber inside in an alcoholic water solution 40% in this invention, is 2 1m of film surface products. It is more desirable that it is 0.5mg or less of hits. Such a hollow fiber can be obtained as follows.
[0021] The polysulfone system hollow filament mold blood purification film of this invention is produced by the dryness-and-moisture type spinning method mentioned later. It is eating into PVP and (b) polysulfone system polymer particle which exist in the film just behind spinning between (a) polysulfone system polymer particles, and are easily removed by processing of rinsing or heat rinsing weakly, and in processing of rinsing or heat rinsing, although it is hard to remove, it is presumed that PVP which can be eluted, and PVP by which extract clearance is not carried out by eating into (c) polysulfone system polymer particle exist. By the Prior art, even if it can carry out the washing clearance of (a) type PVP, clearance of (b) type PVP is considered that are not enough, for this reason PVP which has not insolubilized from the film of a under [an activity] is eluted gradually. In this invention, in order to decrease elution of PVP from the film, the approach of carrying out washing clearance of (b) type PVP as much as possible is proposed.
[0022] The 1st approach of washing clearance of this invention is the approach of washing the polysulfone system hollow fiber which produced the film with the good solvent of a polysulfone system polymer, and the mixed solvent of a poor solvent. As a matter of course, this partially aromatic solvent dissolves PVP which that mixing ratio is set as the range in which a polysulfone system polymer is not dissolved, and has not insolubilized. With such a mixed solvent, by causing a swelling operation in a polysulfone system polymer particle, softening the polysulfone system polymer of a film surface, and improving the floating diffusibility of PVP etc., the inside of the film can be defecated by drawing out PVP from a polysulfone system polymer particle and the interior of a compact layer, consequently it is thought that elution can be reduced to altitude.

[0023] dimethylacetamide (henceforth DMAC), a N-methyl-2-pyrrolidone, dimethyl sulfoxide (henceforth DMSO), dimethylformamide, etc. can be illustrated, and independent as a good solvent of a polysulfone system polymer used by the 1st approach, -- or it is mixed and used. DMAC and/or DMSO are used preferably especially. Moreover, as a poor solvent of a polysulfone system polymer, although water, isopropyl alcohol, ethanol, propyl propylene glycol, tetraethylene glycol, etc. can be illustrated, water is used preferably especially. Although the mixing ratio of the good solvent and poor solvent of this polysulfone system polymer does not generally have ********** since conditions change with the classes or processing temperature of a solvent, it is desirable to use the good solvent of a polysulfone system polymer as 30 - 95 % of the weight. For example, 30 - 60% of the weight of a DMAC water solution, 30 - 60% of the weight of N-methyl pyrrolidone water solution, 50 - 95% of the weight of a DMSO water solution, etc. are used. moreover, the good solvent of a polysulfone system polymer and the poor solvent of a polysulfone system polymer -- independent -- it is not necessary to use it -- each of two sorts or the good solvent beyond it, or a poor solvent -- the mixed solution of mixture is sufficient. Although the temperature of arbitration is sufficient as it, when using the water solution of the good solvent of a polysulfone system polymer, below the boiling point of water is desired on actuation, it is the range where 10-98 degrees C is desirable, processing temperature has still more desirable 30-98 degrees C, and 50-95 degrees C is desirable [temperature].

[0024] The 2nd approach of washing clearance of this invention is the approach of washing the polysulfone system hollow fiber which produced the film with a hot alcohols solvent. The polysulfone system polymer particle which constitutes the film swells, and while PVP incorporated weakly becomes easy to separate, the diffusion rate of PVP becomes large. For this reason, in processing of rinsing or heat rinsing, it is presumed that washing clearance of PVP which is hard to remove is carried out. Therefore, when processing temperature is low, washing removing becomes inadequate, the higher one is desired, but if too high, change of membrane structure will take place and membraneous ability will be changed. For this reason, in this invention, washing processing at 130-160 degrees C is desired. It is 135-155 degrees C preferably, and is 140-150 degrees C still more preferably.

[0025] Although the alcohols solvent which can be used by this invention is the good solvent of PVP and all the things that have a swelling operation to a polysulfone system polymer are raised, the alcohols solvent which has the boiling point or the decomposition point 130 degrees C or more from the simple nature of actuation and equipment is desirable. A glycerol is used preferably especially. Little direction is desirable, and the moisture regain of an alcohols solvent can recommend 5% or less, is desirable, and is still more desirable. [0.5% or less of] [1% or less of] It is not necessary to let the process of rinsing or heat rinsing pass beforehand, and to use PVP which is easy to be removed, and the thing which removed the solvent of a spinning undiluted solution as a polysulfone system hollow fiber which the 1st approach and 2nd approach produced. Even if the solvent of a spinning undiluted solution remains, it is guessed that it is also more effective for washing clearance of PVP to be in the condition that the film expanded.

[0026] Moreover, the 1st approach and 2nd approach can illustrate the following approach as an art. (1) Make the temperature of arbitration heat this film in the condition of having made the penetrant remover immersed. (2) Make the film immersed in the penetrant remover adjusted to laying temperature. (3) Carry out the shower of the penetrant remover adjusted to laying temperature to the film. (4) Make it run the film in the penetrant remover adjusted to laying

temperature. What is necessary is to be possible and just to contact enough the penetrant remover by which the polysulfone system hollow fiber which produced the film in short was adjusted to laying temperature by any approach. By the approach of (1) - (3) which changes with arts and serves as batch operation, 10 minutes or more of the processing time are desirable, and it is still more desirable. [of 30 minutes or more] Moreover, in (4) used as consecutive operation, it is required for the residence time to be 15 seconds or more, and 20 seconds or more are still more desirable. It is desirable to carry out washing clearance of the solvent used after processing by rinsing, heat rinsing, etc. as a matter of course.

[0027] When the internal surface of the polysulfone system hollow filament mold blood purification film of this invention is observed with a scanning electron microscope, the fibrous polysulfone system polymer (fibril) forms the structure where it has gathered together with hollow filament fiber shaft orientations, and there is a gap between fibrils in some places. Between this fibril is torn by the conditions of film production, and that gap becomes large according to them so that it may mention later. In the hollow fiber which has such an internal surface, while surface smooth nature is lost and haemocompatibility worsens, the clearance nature of a solute molecule is also affected bad. For this reason, in the hollow fiber of this invention, a hollow fiber internal surface is expected not to have the torn gap 0.8 micrometers or more.

[0028] It opts for sieving of a solute molecule with solute molecular size and the magnitude of a membranous hole. That is, although a solute molecule smaller than a membranous aperture can penetrate the film, a bigger solute molecule than a membranous aperture cannot be penetrated. Although sieving of a solute molecule breaks out by this principle, when membrane structure is the uneven film and an aperture becomes small in the direction of a film cross section, sieving takes place by the selection detached core as used in the field of this invention. Generally, the selection detached core as used in the field of [by the way a film aperture is small, therefore] this invention of structure with a precise polymer part can be deciphered from the transmission electron microscope image of a film cross section. That is, it asks for the rate (ratio of organized labor) that perform a break and image analysis by fixed width of face, and a polymer part occupies the image of the transmission electron microscope of a film cross section. If this actuation is turned to a hollow fiber outside and performed from the hollow fiber inside, distribution of the ratio of organized labor in the direction of a hollow fiber membrane cross-section will become clear. Pore size distribution was in the film so that it might mention later, but when image analysis of the selection detached core was carried out having used width of face of image analysis as 0.5-1.0 micrometers by this invention in consideration of it, from the highest value of a ratio of organized labor, it was defined as the part in less than 30% of range, and the thickness was measured.

[0029] A membranous fractionation property is explained by the multilayer-structure model. That is, the structure in which the layer of a large number which sliced the film (vertically [as opposed to / Therefore / a film cross section]) to parallel to the film surface carried out the laminating is assumed. A solute molecule is screened for every layer of this, and I think that multistage filtration is performed by the whole film. Although average apertures differ for every layer, since the aperture in the layer has distribution when one layer is taken up, there is not effectiveness which a solute screens but only the layer of min [aperture / average] can catch the big solute molecule through which the layer to which the average aperture became large a little has also passed. In other words, the solute molecule with which the average aperture has passed through the big place of an aperture in the small layer is fully caught with a hole with size

smaller than a solute molecule, although the average aperture became a little large. Therefore, as a selection detached core, even the layer [layer / min / aperture / average] to which it became large a little is effective.

[0030] The thickness of a selection detached core is important for the sharpness of a fractionation property. If a little average aperture tends to be raised and it is going to improve permeability of the clearance matter when a selection detached core is thin, it will become easy to penetrate the albumin which is a useful plasma protein. If distribution of an aperture is in a selection detached core and an average aperture is raised, it will be guessed for the holes which can penetrate albumin according to it also increasing in number. Since there is no another selection detached core which catches the albumin once leaked from the big part of an aperture when a selection detached core is thin, the film will be penetrated as it is. Moreover, also when a structure defect arises in a selection detached core under the effect of slight fluctuation of spinning conditions etc., leak of the amount matter of macromolecules becomes remarkable especially. On the other hand, about membrane structure, when a selection detached core is thick, even if comparatively loose, if the thickness is thick, there will be little leak of albumin, namely, a molecular weight fractionation property will become Sharp. Since the membranous selection detached core is thick as for this, even if albumin penetrates in one layer, it is because the probability which is caught in some layer of a selection detached core, and penetrates the film as a result becomes low. However, since transparency resistance will become large too much if a selection detached core is too thick, in this invention, it is required to be 2 micrometers - 15 micrometers, it is 3 micrometers - 12 micrometers still more preferably, and 5 micrometers - 10 micrometers are more desirable.

[0031] Although it may be in the hollow fiber inside, may be located in a cross-section core, or may be located on both the hollow fiber inside and the hollow fiber outside or any are sufficient as it at a screening efficiency, as for the location of a selection detached core, it is desirable that a selection detached core is in the hollow fiber inside in this invention in order to prevent encroachment on the film of the protein in the blood leading to plugging of a film inner hole generally, since blood is poured by the hollow fiber inside.

[0032] On the occasion of film production of the polysulfone system hollow filament mold blood purification film in this invention, the dryness-and-moisture type film production technique which is a technique generally known from before can be used. That is, a polysulfone system polymer and PVP are first dissolved in a common solvent at both, and a uniform spinning undiluted solution is adjusted. As a common solvent which dissolves such both polysulfone system polymers and PVP, the solvent which consists of a solvent of varieties, such as DMAC, DMSO, a N-methyl-2-pyrrolidone, dimethylformamide, a sulfolane, and dioxane, or the two or more above-mentioned sorts of mixed liquor is mentioned, for example. Moreover, additives, such as water, may be added to a spinning undiluted solution for aperture control.

[0033] Although a big macro void comes to appear notably inside the film when spinning undiluted solution viscosity is too low, in the case of the hollow fiber for blood purification, in the hollow fiber which blood coagulation will become easy to happen during hemodialysis, and will be used for hemodialysis if many such macro voids exist, it is desirable that there is no macro void. As for the macro void said here, the overall diameter says a thing 5 micrometers or more among the space in which a polymer does not exist within the film. On the other hand, it undiluted solution viscosity becomes high too much, the pressure in front of a spinneret is improved too much, and stable spinning becomes impossible. Therefore, in this invention, 1500 - 6000mPa and a second are required for spinning undiluted solution viscosity, and the range of

2000 - 4000mPa and a second is desirable. With the viscosity said by this invention, a spinning undiluted solution is measured with the viscometer of a rotating type at the spinneret temperature and this temperature under film production conditions.
[0034] Depending on the polysulfone system polymer in the molecular weight of PVP, and a spinning undiluted solution and the concentration of PVP, the temperature of a spinning undiluted solution, etc., as for the viscosity of a spinning undiluted solution, every factor does the serious effect for formation of membrane structure. In this invention, undiluted solution viscosity is adjusted to the above-mentioned range by choosing the raw material to be used appropriately and setting up the conditions of concentration and temperature. Since membranous formation will become difficult if too few, film reinforcement becomes weak too much or phenomena, like an aperture will worsen [spinning nature] too much small if many [too] arise, as for the addition of polysulfone system polymer system resin, it is desirable that it is 15 - 20 % of the weight, and it is still more desirable that it is 16 - 19 % of the weight. However, what is necessary is it not to be absolute that it is this range, and to be also able to enlarge making it smaller than this range depending on the description of the hollow fiber made into the object, and just to choose the optimal combination suitably, since the shape of membranous changes also by changing other spinning conditions.
[0035] The object which adds PVP to a spinning undiluted solution is making PVP remain in a hollow fiber and giving a hydrophilic property to the film. Therefore, the molecular weight of PVP to be used is important. That is, when the molecular weight of PVP is too small, since this PVP is easily eluted from the film, in order to make PVP required to give a hydrophilic property to a hollow fiber remain in a hollow fiber, it is necessary to add a lot of PVP to a spinning undiluted solution at the time of the coagulation of a spinning undiluted solution, and washing of the obtained hollow fiber. for this reason, K-value with which the one where molecular weight is larger is desirable for raising the survival rate to the hollow fiber of PVP, and is defined as it by the degree type -- 88-95 -- 89-94 are preferably good.
[0036]
[Formula 1]

$$K\text{値} = \frac{\sqrt{300C\log Z + (C + 1.5C\log Z)^2} + 1.5C\log Z - C}{0.15C + 0.003C^2}$$

Here, Z is the rate of relative viscosity of the solution of concentration C, and C is the concentration of % (weight/capacity).
[0037] The relative amount of the polysulfone system polymer in a spinning undiluted solution and PVP is very important when determining the internal-surface PVP concentration of the hollow fiber obtained. The ratio of the absolute magnitude of the polysulfone system polymer which exists in the coagulation side by contact of the liquid in hollow and a spinning undiluted solution in the internal surface of a hollow fiber in order that rapid coagulation may start, and PVP is because it is fixed to an internal surface as it is. When there are too few weight ratios of PVP to the polysulfone system polymer in a spinning undiluted solution, surface PVP concentration does not go up. When there are too many weight ratios of PVP, membranous reinforcement becomes weak and it becomes impossible moreover, to disregard the elution volume of PVP from the film to a polysulfone system polymer. then, the weight ratio of PVP [as opposed to / when it is going to make PVP concentration of a hollow filament internal surface 30% - 45%, with the reinforcement beyond the need maintained / the polysulfone system polymer in a spinning undiluted solution] -- 0.25 thru/or 0.5 -- it is preferably required 0.3

thru/or 0.48, and to be 0.35 thru/or 0.45 still more desirably.
[0038] That what is necessary is for the liquid in hollow to be able to use the coagulation liquid which made water or water the subject, and just to decide the presentation etc. according to the membraneous ability of the hollow fiber made into the object, although there is no ********** generally, generally the mixed solution of the solvent and water which were used for the spinning undiluted solution is used suitably. For example, although 0 - 60% of the weight of a DMAC water solution etc. is used, it is especially desirable that it is 0 - 40 % of the weight. It rolls round, after making the water installed in the spinning port lower part after extruding simultaneously the liquid in hollow for facing producing a hollow fiber and making said spinning undiluted solution and this spinning undiluted solution solidify from this spinning port using the duplex spinning port of a tube in orifice mold in the air and making it run the 20-80cm free-running section immerse and solidify into the coagulation bath made into a subject.
[0039] the rate of a spinning draft as used in the field of this invention -- the annular slit of the duplex spinning port of a tube in orifice mold -- it is the value which is the ratio of regurgitation linear velocity in case a spinning undiluted solution is breathed out, and the rolling-up rate of a hollow fiber, and broke the rolling-up rate by regurgitation linear velocity of a spinning undiluted solution from the mouthpiece. In the case of the low rate of a spinning draft, it is necessary to make slit width of a spinneret that much narrow. In the case of the hollow fiber for blood purification, the range of the thickness usually used is 20-60 micrometers. For this reason, when the rate of a spinning draft is low, since the regurgitation linear velocity of an undiluted solution will increase and the pressure loss in a spinneret will become large if spinning speed is raised, spinning tends to become instability. Moreover, since the regurgitation nonuniformity of an undiluted solution arises, the variation in turbulence, permeable ability, and the solute transparency engine performance also becomes [membrane structure] large. Furthermore, since slit width is narrow, problems, like that the alignment of a spinneret becomes difficult and the creation of a spinneret itself becomes difficult and it becomes high cost are pointed out. On the contrary, while it rolls round to the regurgitation linear velocity of the undiluted solution from a spinneret, and a hollow filament internal surface will solidify directly under a spinneret when a rate is too quick if the rate of a spinning draft is too high namely, it becomes the configuration by which the compact layer of a film internal surface was tore by being pull strongly, and since it becomes easy to generate the hole which has an extraordinarily big aperture, the leak problem of the albumin which is useful protein arises. This problem is stopping undiluted solution viscosity low by making high temperature of the spinning undiluted solution into which the presentation of a spinning undiluted solution is changed etc., and a certain extent is not enough although it is improvable. Therefore, in this invention, 1.1-1.9 are required for the rate of a spinning draft, and it is desirable that it is the range of 1.1-1.5.
[0040] The regurgitation linear velocity of the undiluted solution said here is linear velocity in case a spinning undiluted solution is breathed out from a spinneret at the time of spinning, and is the value which broke the amount of discharge flow of the spinning undiluted solution per unit time amount by the undiluted solution regurgitation cross section of a spinneret. If the regurgitation linear velocity of an undiluted solution becomes large, the regurgitation nonuniformity of an undiluted solution will become large, the hole which has a big aperture by membranous structure nonuniformity will form, and leak of albumin will arise. At this invention, the regurgitation linear velocity of an undiluted solution needs to be 90 or less m/min, it is desirable that they are 70 or less m/min, and it is more more desirable still that they are 60 or less m/min.

[0041] In order to control a selection detached core, a film production process as shown below is important. First, as a result of coagulation's progressing gently since the coagulation force becomes weak if the class and concentration of the liquid in hollow are important and make high solvent concentration in the liquid in hollow, precise condensation structure cannot be taken but a selection detached core becomes **** structure. Next, if the viscosity of a spinning undiluted solution is important and viscosity is high, migration of a polysulfone system polymer will be suppressed at the time of coagulation, and a selection detached core will become thick compared with the case where viscosity is low, under these conditions. Depending on the concentration of the polysulfone system polymer in the molecular weight of a hydrophilic macromolecule, and a spinning undiluted solution, and a hydrophilic macromolecule, the temperature of a spinning undiluted solution, etc., as for the viscosity of a spinning undiluted solution, every factor does the serious effect for formation of a selection detached core. Moreover, it is better to raise the rate of a spinning draft by the factor also with an important spinning draft, in order to give a thick selection detached core. Although there is a solvent used for the distance of the free-running section from a spinneret to a coagulation bath, spinneret size, the temperature of a coagulation bath, a presentation and spinning speed, and a spinning undiluted solution in addition to this, it is necessary to set up the factor which affects formation of a selection detached core in consideration of balance with the penetrable ability of a solute, the object, etc.
[0042] After treatment of the hollow fiber which spinning was carried out as mentioned above and rolled round is carried out by the well-known approach. That is, after removing a solvent and superfluous PVP by washing by hot water etc. and giving a glycerol if needed, dry heat desiccation is carried out. Moreover, after rolling round a hollow fiber, after treatment is not carried out, but the approach of rolling round, after carrying out dry heat desiccation, washing by hot water etc. and is also within the limits of this invention, an important thing adjusts spinning undiluted solution viscosity to 1500 - 6000mPa and a second by this invention, the regurgitation linear velocity from a spinneret is the conditions of 90 or less m/min, and it is making the rate of a spinning draft or less into 1.1 to 1.9.
[0043]
[The mode of implementation of invention] Although an example and the example of a comparison are used for below and this invention is explained to it at a detail, thereby, this invention is not limited at all. The amount of water penetration and sieve multiplier in this invention are measured as follows. That is, assembly molding of the mini module (25cm of effective length) which consists of 100 dried polysulfone system selection transparency hollow fibers was carried out, and the amount of water penetration was measured in the unit of ml/Hr/m2 / mmHg with the Floe process also as that of the flow and pressure requirement of 200mmHg. Then, beta2-MG and the sieve multiplier of albumin were further measured using cow plasma. Using ORIENTECTENSILON;RTC -1210, yarn reinforcement was pulled until it fractured the hollow fiber, and it made reinforcement maximum load which took then.
[0044]
[Example 1] The uniform spinning undiluted solution which consists of the polysulfone resin (Amoco performance products company make, P-1700) 17 weight section, the polyvinyl-pyrrolidone (BASF make, K-92) 7 weight section, and the DMAC76 weight section was created. This spinning undiluted solution viscosity was 3400 mPa-s at 65 degrees C. having kept this spinning undiluted solution at 65 degrees C -- the liquid in hollow of 15%DMAC -- the slit width of 59.5 micrometers -- annular -- from the mouthpiece, it was immersed in discharge and underwater [which were prepared caudad 60cm / 55-degree C], and rolled round at the rate of

70 m/min. Since the discharge quantity of a spinning undiluted solution was adjusted so that the hollow fiber thickness at the time of desiccation might be doubled with 45 micrometers, the regurgitation linear velocity of an undiluted solution became 49.3 m/min, and the rate of a draft was 1.42. The shower of 40% of the weight of the DMAC water solution which warmed the acquired hollow fiber bundle at lowering and 85 degrees C was carried out for 80 minutes. Then, hot water washing was carried out at 90 degrees C, it was immersed in the glycerol water solution 20%, and the glycerol was made to adhere. Subsequently, hot air drying was carried out at 75 degrees C for 11 hours. Then, the hollow fiber was made immersed in the water solution in which 600 ppm of sodium disulfite and 300 ppm of sodium carbonates were dissolved, the gamma ray of 25kGy was irradiated, and the polysulfone system blood purification film was obtained. The osmium tetroxide water solution dyed the obtained hollow fiber, embedding was carried out with the epoxy resin after dehydration, about 60nm ultrathin section was created after hardening using ultramicrotome, and TEM (JEM2000FX) observation was performed. The ratio of organized labor was measured towards the outside-surface side at intervals of 0.7 micrometers using the obtained TEM image with image-analysis equipment (IP-1000: Asahi Chemical Co., Ltd. make) from the hollow fiber internal-surface side. A measurement result and a membranous assessment result are shown in a table 1. Moreover, the situation of the internal surface of this film is shown in drawing 1 . There is no torn structure and it has become a smooth front face.

[0045]

[Example 2] The polysulfone system blood purification film was obtained like the example 1 except having carried out the shower of the 130-degree C glycerol for extract washing of a hollow fiber for 3 hours instead of 80 degrees C and the shower for 80 minutes in 40%DMAC water solution. The obtained result is shown in a table 1.

[Example 3] The polysulfone system blood purification film was obtained like the example 1 except not performing extract washing by the shower for 80 degrees C and 80 minutes in 40%DMAC water solution. The obtained result is shown in a table 1.

[0046]

[Example 4] The uniform spinning undiluted solution which consists of the polysulfone resin (Amoco performance products company make, P-1700) 17 weight section, the polyvinyl-pyrrolidone (BASF make, K-89) 7 weight section, and the DMAC76 weight section was created. This spinning undiluted solution viscosity was 1650 mPa-s at 80 degrees C. having kept this spinning undiluted solution at 80 degrees C -- the liquid in hollow of 15%DMAC -- the slit width of 59.5 micrometers -- annular -- it was immersed in discharge and underwater [which were prepared caudad 60cm / 55-degree C] from the mouthpiece, and rolled round by 70 m/min. After that, the polysulfone system blood purification film was obtained like the example 1. The obtained result is shown in a table 1.

[0047]

[Example 5] The uniform spinning undiluted solution which consists of the polysulfone resin (Amoco performance products company make, P-1700) 16 weight section, the polyvinyl-pyrrolidone (BASF make, K-89) 7.8 weight section, and the DMAC76.2 weight section was created. This spinning undiluted solution viscosity was 2500 mPa-s at 70 degrees C. having kept this spinning undiluted solution at 70 degrees C -- the liquid in hollow of 15%DMAC -- the slit width of 59.5 micrometers -- annular -- it was immersed in discharge and underwater [which were prepared caudad 60cm / 55-degree C] from the mouthpiece, and rolled round by 70 m/min. After that, the polysulfone system blood purification film was obtained like the example 1. The obtained result is shown in a table 1.

[0048]
[Example 6] The uniform spinning undiluted solution which consists of the polysulfone resin (Amoco performance products company make, P-1700) 17 weight section, the polyvinyl-pyrrolidone (BASF make, K-92) 5.5 weight section, and the DMAC78.5 weight section was created. This spinning undiluted solution viscosity was 2400 mPa-s at 50 degrees C. having kept this spinning undiluted solution at 50 degrees C -- the liquid in hollow of 15%DMAC -- the slit width of 59.5 micrometers -- annular -- it was immersed in discharge and underwater [which were prepared caudad 60cm / 55-degree C] from the mouthpiece, and rolled round by 70 m/min. After that, the polysulfone system blood purification film was obtained like the example 1. The obtained result is shown in a table 1.
[0049]
[Example 7] The uniform spinning undiluted solution which consists of the polysulfone resin (Amoco performance products company make, P-1700) 17 weight section, the polyvinyl-pyrrolidone (BASF make, K-89) 6.3 weight section, and the DMAC76.7 weight section was created. This spinning undiluted solution viscosity was 2820 mPa-s at 55 degrees C. having kept this spinning undiluted solution at 55 degrees C -- the liquid in hollow of 15%DMAC -- the slit width of 59.5 micrometers -- annular -- it was immersed in discharge and underwater [which were prepared caudad 60cm / 55-degree C] from the mouthpiece, and rolled round by 70 m/min. After that, the polysulfone system blood purification film was obtained like the example 1. The obtained result is shown in a table 1.
[0050]
[The example 1 of a comparison] The polysulfone system hemodialysis film was obtained like the example 6 except not irradiating a gamma ray. The obtained result is shown in a table 1.
[The example 2 of a comparison] It was underwater immersed instead of making a hollow fiber immersed in the water solution in which 600 ppm of sodium disulfite and 300 ppm of sodium carbonates were dissolved, and the polysulfone system hemodialysis film was obtained like the example 6 except having irradiated the gamma ray of 50kGy. The obtained result is shown in a table 1.
[0051]
[The example 3 of a comparison] a spinning undiluted solution -- the liquid in [15% of] hollow -- the slit width of 59.5 micrometers -- annular -- instead of carrying out the regurgitation from a mouthpiece -- the slit width of 125 micrometers -- annular -- the polysulfone system blood purification film was obtained like the example 1 except having made it breathe out from a mouthpiece. The obtained result is shown in a table 1. Moreover, the rate of a draft was 3.2 at this time. The internal surface of this film has structure torn greatly under the effect of a draft, and shows that situation to drawing 2 .
[The example 4 of a comparison] a spinning undiluted solution -- the liquid in hollow of 15%DMAC -- the slit width of 59.5 micrometers -- annular -- instead of carrying out the regurgitation from a mouthpiece -- the slit width of 50 micrometers -- annular -- the polysulfone system blood purification film was obtained like the example 1 except having made it breathe out from a mouthpiece. The obtained result is shown in a table 1. Moreover, the rate of a draft was 1.0 at this time. Although there is no structure which was torn since the internal surface of this film has the low draft, it is the effect considered to be the regurgitation nonuniformity of an undiluted solution, and structure nonuniformity is seen. The situation is shown in drawing 3 .
[0052]
[The example 5 of a comparison] The uniform spinning undiluted solution which consists of the

polysulfone resin (Amoco performance products company make, P-1700) 17 weight section, the polyvinyl-pyrrolidone (BASF make, K-92) 3.5 weight section, and the DMAC79.5 weight section was created. This spinning undiluted solution viscosity was 1250 mPa-s at 50 degrees C. having kept this spinning undiluted solution at 50 degrees C -- the liquid in hollow of 15%DMAC -- the slit width of 59.5 micrometers -- annular -- it was immersed in discharge and underwater [which were prepared caudad 60cm / 55-degree C] from the mouthpiece, and rolled round by 70 m/min. After that, the polysulfone system blood purification film was obtained like the example 1. The obtained result is shown in a table 1.

[0053]

[A table 1]

表1

	バルクPVP (%)	ESCA:PVP (%)	溶出PVP (mg/m2)	Alb SC (%)	β2−Mg (%)	透水 (＊)	残血	緻密層 (μm)	引き裂き	強度 (g/hf)	可溶性PVP (mg/g-HF)
実施例1	7.0	38	0.25	0.003	0.64	210	○	10.5	無し	17.1	8.0
実施例2	7.1	38	0.26	0.003	0.64	205	○	10.6	〃	17.2	8.3
実施例3	8.9	39	1.01	0.002	0.55	175	○	11.2	〃	17.1	11.9
実施例4	5.0	35	0.27	0.004	0.68	287	○	4.8	〃	19.2	6.9
実施例5	8.1	44	0.25	0.004	0.61	165	○	8.2	〃	16.3	9.6
実施例6	4.5	30	0.41	0.005	0.70	514	○	9.2	〃	19.8	7.8
実施例7	5.5	33	0.30	0.002	0.68	222	○	7.5	〃	19.0	7.8
比較例1	4.8	31	2.20	0.003	0.63	229	○	9.5	〃	19.8	43.0
比較例2	4.8	31	0.10	0.003	0.67	209	×	9.5	〃	19.8	0.2
比較例3	4.6	32	0.25	0.010	0.69	255	×	9.3	有り	19.8	8.0
比較例4	7.3	38	0.28	0.009	0.68	245	○	9.2	ムラ	17.0	8.1
比較例5	3.2	24	0.95	0.011	0.85	702	×	6.8	〃	21.2	2.0

(＊)ml／Hr／m2／mmHg

[0054] Residual blood assessment was carried out about the hollow fiber of examples 1-7 and the examples 1-5 of a comparison. That is, 120 hollow fibers of 16cm length were constructed to the module, and 20ml of physiological salines washed. Then, the blood taken out from the dog carotid artery through the peristaltic pump was shunted toward the hollow filament inside ten by 2ml flow rate for /. After extruding blood by 5ml of physiological salines, the module was disassembled and the degree of residual blood was evaluated. Consequently, by the hollow filament of the examples 2 and 3 of a comparison, and 5**, although residual blood was accepted, it remained [whether there is almost any residual blood and] in the hollow fiber of the other examples of a comparison, and an example a little.

[0055]

[Effect of the Invention] As stated above, the polysulfone system blood purification film of this invention improves haemocompatibility, and there are very few elution volumes of the polyvinyl pyrrolidone by the side of blood, and it is the hollow fiber which was excellent in molecular weight fractionation nature further. By this invention, a very significant artificial kidney can be offered in future dialysis treatment.

TECHNICAL FIELD

[Field of the Invention] This invention relates to the polysulfone system hollow filament mold blood purification film and its manufacture approach. In detail, it is related with the polysulfone system blood purification film with which haemocompatibility and a separation property were improved, and its manufacture approach.

PRIOR ART

[Description of the Prior Art] In recent years, the ultrafiltration method which is the separation technology using a permselectivity demarcation membrane, reverse osmosis, a gas separation method, etc. are put in practical use in various kinds of fields, and the demarcation membrane made from the raw material which fits the various applications respectively is marketed. As a raw material of a permselectivity demarcation membrane, polymers, such as a cellulose type, a cellulose acetate system, a polyamide system, a polyacrylonitrile system, a polyvinyl alcohol system, a polymethylmethacrylate system, a polysulfone system, and a polyolefine system, are used. Since physicochemical qualities, such as thermal resistance, acid resistance, alkali resistance, and oxidation resistance, are excellent especially, the polysulfone system polymer attracts attention also especially as medical application in recent years and an industrial use demarcation membrane raw material.

[0003] However, since a polysulfone system polymer is a hydrophobic raw material, the permselectivity demarcation membrane made from this does not have good water wettability compared with the permselectivity demarcation membrane made from the hydrophilic polymer. For this reason, when it considers as medical application, adsorption of a plasma protein tends to take place, and since the omission of air bubbles is bad, the fault of resulting in blood coagulation because the air bubbles which remained into the film activate ejection and a platelet into blood is pointed out.

[0004] Then, the examination for giving a hydrophilic property to the permselectivity demarcation membrane which consists of a polysulfone system polymer, and raising water wettability is made, and the permselectivity demarcation membrane which made the polysulfone system polymer contain a hydrophilic polymer, and its process are proposed as the one approach. However, if there are few contents of a hydrophilic polymer, water wettability will worsen, blood coagulation is caused, and when objection has many contents of a hydrophilic polymer, there is a trouble that the elution volume of the hydrophilic polymer from the film after film production increases.

[0005] JP,61-238306,A and 63-97666 -- a polysulfone system polymer, a hydrophilic polymer, and this polysulfone system polymer -- receiving -- a non-solvent -- or -- a swelling agent -- although the manufacture approach of the polysulfone system demarcation membrane using the system which added the additive as a film production undiluted solution is indicated, there is no publication of the approach of reducing elution of a hydrophilic polymer. Moreover, by performing radiation treatment and/or heat treatment for the polysulfone system demarcation membrane manufactured by the above-mentioned approach to JP,63-97205,A, 63-97634, and JP,4-300636,A, a hydrophilic polymer is insolubilized and the method of reducing elution of a hydrophilic polymer is indicated. However, probably because a hydrophilic polymer insolubilizes according to this bridge formation, haemocompatibility worsens.

[0006] In JP,6-165926,A, processing with the solution which has a poor solvent operation for the polysulfone system hollow fiber containing polyglycols and a vinyl-pyrrolidone system polymer

to rinsing, heat rinsing processing, and this polysulfone system polymer is performed, and the method of manufacturing the hollow fiber film is indicated. However, processing with the solvent which has this poor solvent operation is performed at 90 degrees C, and extract clearance is not enough.

[0007] It is related with a spinning draft. To JP,5-54373,B A hydrophobic polymer, Carried out spinning of the undiluted solution of hypoviscosity which consists of hydrophilic polymers and those common solvents, and were manufactured. The process of the hollow fiber for blood processing which contains a hydrophilic polymer one to 10% of the weight, and has 3 - 10% of water absorption capacity is indicated. In this It is, when the thing with same rate which comes out of the spinneret of a spinning constituent and generated taking over rate of fiber, i.e., the rate of a spinning draft is 1, is desirable. However, when the rate of a draft is 1 actually, it is difficult to raise spinning speed. If the discharge quantity of an undiluted solution is raised in order to raise spinning speed, the regurgitation linear velocity of that the pressure loss of a spinneret becomes large and a spinning undiluted solution will increase, and problems, like that become easy to produce the regurgitation unevenness of a spinning undiluted solution, and spinning becomes instability and membrane structure is confused will arise. Moreover, although it is that a nozzle draft is usually set as the range of 2-5 in JP,6-165926,A since structure will become instability if a nozzle draft is enlarged extremely or it is made small, if the rate of a draft exceeds 2, it will become the structure where the hollow filament internal surface was torn, and troubles, such as becoming easy to leak the albumin which is useful protein, are pointed out.

[0008] In recent years, as a cause of dialysis complication, low-molecular proteins, such as beta2-microglobulin (beta2-MG), are mentioned, and highly efficient permeable membrane which can remove these from blood efficiently is desired. In the above-mentioned Prior art, sufficient examination to fractionation nature is not made and it is not necessarily a satisfaction **** thing. That is, it is because leak of useful proteins, such as albumin, will pose a problem if the membranous transparency engine performance is improved in order to improve clearance of low-molecular protein.

EFFECT OF THE INVENTION

[Effect of the Invention] As stated above, the polysulfone system blood purification film of this invention improves haemocompatibility, and there are very few elution volumes of the polyvinyl pyrrolidone by the side of blood, and it is the hollow fiber which was excellent in molecular weight fractionation nature further. By this invention, a very significant artificial kidney can be offered in future dialysis treatment.

TECHNICAL PROBLEM

[Problem(s) to be Solved by the Invention] This invention cancels the trouble of the conventional technique, improves haemocompatibility, and there is very little elution of the polyvinyl pyrrolidone by the side of the internal surface of a hollow fiber, and, moreover, it aims at offering the polysulfone system blood purification film which improved the membranous separation property, and its manufacture approach.

MEANS

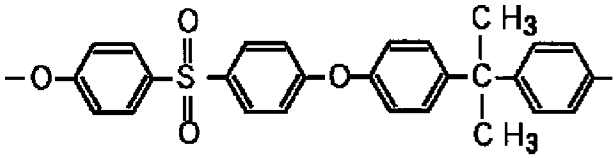
[Means for Solving the Problem] As a result of inquiring wholeheartedly that this invention persons should attain the above-mentioned technical problem, in the hollow filament-like polysulfone system hollow filament mold blood purification film containing a polyvinyl pyrrolidone (henceforth PVP), by making a part of PVP into a condition insoluble in water, and making suitable PVP concentration of a hollow fiber internal surface, there was little elution of PVP from an internal surface, it was excellent in haemocompatibility, and found out that a pure hollow fiber could moreover be offered. Moreover, by extracting PVP with a suitable solvent, the hollow fiber was washed and elution of PVP from an internal surface found out still fewer things for which a pure hollow fiber can be offered. Furthermore, while the thickness with the effectiveness which screens a solute molecule from the spinning undiluted solution which has suitable viscosity substantially in the film by carrying out spinning at the suitable rate of a spinning draft of a selection detached core was appropriately controllable, it tears to a hollow fiber internal surface, there is no structure, and it found out that the sharp polysulfone system blood purification film of the fractionation nature which can perform clearance of an undesired substance and recovery of the useful matter efficiently could be offered.

[0011] That is, in the polysulfone system hollow filament mold blood purification film which the selection detached core in which this invention has isolation substantially exists in a hollow fiber internal-surface side, and contains a polyvinyl pyrrolidone, it contains 10% of the weight, and 5 of this polyvinyl pyrrolidone thru/or 50% are fusibility at water, and a polyvinyl pyrrolidone is the polysulfone system blood purification film characterized by 1 thru/or the concentration of the polyvinyl pyrrolidone of an internal surface being in 30 to 45% of range.

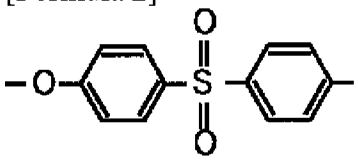
[0012] After this invention contains a polysulfone system polymer 15 to 20% of the weight again and the weight ratio of the polyvinyl pyrrolidone to a polysulfone system polymer carries out spinning of the hollow fiber using the polymer solution which are 0.25-0.5, it is the manufacture approach of the polysulfone system hollow filament mold blood purification film characterized by making a part of polyvinyl pyrrolidone in this hollow fiber insolubilize by the physicochemical approach.

[0013] The manufacture approach of the polysulfone system blood purification film characterized by this invention extracting and washing a polyvinyl pyrrolidone with the solvent or alcohols solvent which is a partially aromatic solvent of the good solvent and poor solvent of a polysulfone system polymer about the hollow fiber behind spinning, and dissolves a polyvinyl pyrrolidone further, The viscosity which dissolved the polysulfone system polymer and the polyvinyl pyrrolidone in these common solvents and the spinning undiluted solution of 1500 - 6000mPa and a second It is the manufacture approach of the polysulfone system hollow filament mold blood purification film characterized by carrying out spinning with the rates 1.1-1.9 of a draft, and 90 or less m/min of regurgitation linear velocity. This invention is explained below at a detail.

[0014] The polysulfone system polymer said by this invention is [Formula 1] when an example is given, although it is especially the generic name of the macromolecule connective which has sulfone association and is not limited.



[Formula 2]



It is marketed widely, and since acquisition is also easy, the polysulfone system polymer resin which is alike and has the repeat unit shown is used preferably. It is the brand name of "YUDERU" from the Amoco performance products company, and from BASF, it is marketed by the brand name of an "ultra zone", and, as for the polysulfone resin with the former structure, some classes exist with polymerization degree etc.

[0015] Moreover, PVP of this invention is the water-soluble high molecular compound to which vinyl polymerization of the N-vinyl pyrrolidone was carried out, and is the brand name of a "plus boss" in insertion sequence Py, and is marketed by the brand name of "Kollidon" from BASF, and has the polyvinyl pyrrolidone of some molecular weight, respectively. If the PVP content in a hollow fiber is low, since the PVP concentration of the hollow fiber internal surface in contact with blood will not go up but a membranous hydrophilic property will worsen, blood coagulation becomes easy to happen when blood is contacted. Moreover, although what is necessary is just to make high PVP concentration in the polymer solution used for spinning in order to enlarge the PVP content in a hollow fiber so that it may mention later, the viscosity of a polymer solution also goes up and spinning becomes impossible. For this reason, in this invention, PVP is contained in a hollow fiber in 1 - 10% of the weight of the range in a hollow fiber. It is 2.5 - 8% of the weight of the range preferably.

[0016] The PVP content in a hollow fiber is easily computable with the elemental-analysis value of nitrogen and sulfur. Moreover, thermal cracking gas chromatography can analyze a hollow fiber, and it can ask easily also by analyzing the peak of the PVP origin. PVP is a polymer which is easy to melt into water, and is easily eluted into water or blood from a hollow fiber. Although the elution from a hollow fiber will be thoroughly lost if all PVP to contain is insolubilized, the hydrophilization effectiveness on the front face of the film also becomes weak. For this reason, they are 5 of the whole quantity which is made to insolubilize a part of PVP according to bridge formation, and contains PVP of fusibility in water in this invention at a hollow fiber thru/or 50%. If it is in this range, the elution from a hollow fiber will also be suppressed and the hydrophilization effectiveness on the front face of the film will also be maintained.

[0017] The amount of PVP of fusibility is the amount of PVP in the film which has not insolubilized according to bridge formation, and water is asked for it as follows. That is, a hollow fiber is thoroughly dissolved by the N-methyl-2-pyrrolidone. Subsequently, water is added in this polymer solution and a polysulfone system polymer is settled. The quantum of the amount of PVP in the digestive liquor obtained is carried out with liquid chromatography after standing. A factor important for the haemocompatibility of a hollow fiber is a hydrophilic property on the front face of the film, and the PVP concentration of a film internal surface is important for it in the polysulfone system hollow fiber containing PVP. When surface PVP

concentration is too low, a film front face shows hydrophobicity, a plasma protein tends to adsorb, and the coagulation of blood also tends to take place. That is, haemocompatibility serves as a defect. Conversely, if surface PVP concentration is too high, the elution volume to the blood of PVP etc. will increase and the result which is not desirable will be given for the object and application of this invention. Therefore, the concentration of the film internal surface PVP in this invention is 30% - 45% of range, and is 33% - 40% preferably.

[0018] The PVP concentration of a hollow fiber internal surface is determined by X-ray photoelectron spectroscopy (ESCA). That is, after measurement of ESCA of a hollow fiber internal surface arranges a sample in on a double-sided tape, a cutter cuts it open to fiber shaft orientations, and it puts in order what was extended so that the inside of a hollow fiber might become a table, is made into a sample, and is measured by the usual approach. That is, it asks for the surface concentration (A) of nitrogen, and sulphuric surface concentration (B) from the integrated intensity of N1s and an S2p spectrum C1s and O1s using the relative sensitivity coefficient of equipment attachment, and is surface PVP concentration =Ax100/(Ax111+Bx442). Surface PVP concentration is computed more.

[0019] Elution of PVP from a hollow fiber is estimated by this invention by the elution volume when carrying out the circulation extract of the hollow fiber inner surface in an ethanol water solution 40%. A hollow fiber is included in a module, and it circulates through an ethanol water solution at 37 degrees C 40% to a blood side for 4 hours, and, specifically, is evaluated by measuring the amount of PVP extracted. Although 37-degree C blood is suitable, since past [a minute amount] and the interfering substance have much eluted hydrophilic macromolecule as an extract medium, the quantum of PVP extracted is difficult. Moreover, as an extract medium, the extract force of water is weak and the quantum of PVP extracted is difficult. 40% ethanol water solution is suitable as an extract medium.

[0020] In this invention, a part of PVP is made to insolubilize according to bridge formation as mentioned above, and the elution from a hollow fiber is controlled. Furthermore, the elution volume of the polyvinyl pyrrolidone when elution of PVP from a hollow fiber being controlled and carrying out the circulation extract of the hollow fiber inside in an alcoholic water solution 40% in this invention, is 2 1m of film surface products. It is more desirable that it is 0.5mg or less of hits. Such a hollow fiber can be obtained as follows.

[0021] The polysulfone system hollow filament mold blood purification film of this invention is produced by the dryness-and-moisture type spinning method mentioned later. It is eating into PVP and (b) polysulfone system polymer particle which exist in the film just behind spinning between (a) polysulfone system polymer particles, and are easily removed by processing of rinsing or heat rinsing weakly, and in processing of rinsing or heat rinsing, although it is hard to remove, it is presumed that PVP which can be eluted, and PVP by which extract clearance is not carried out by eating into (c) polysulfone system polymer particle exist. By the Prior art, even if it can carry out the washing clearance of (a) type PVP, clearance of (b) type PVP is considered that are not enough, for this reason PVP which has not insolubilized from the film of a under [an activity] is eluted gradually. In this invention, in order to decrease elution of PVP from the film, the approach of carrying out washing clearance of (b) type PVP as much as possible is proposed.

[0022] The 1st approach of washing clearance of this invention is the approach of washing the polysulfone system hollow fiber which produced the film with the good solvent of a polysulfone system polymer, and the mixed solvent of a poor solvent. As a matter of course, this partially aromatic solvent dissolves PVP which that mixing ratio is set as the range in which a polysulfone system polymer is not dissolved, and has not insolubilized. With such a mixed solvent, by

causing a swelling operation in a polysulfone system polymer particle, softening the polysulfone system polymer of a film surface, and improving the floating diffusibility of PVP etc., the inside of the film can be defecated by drawing out PVP from a polysulfone system polymer particle and the interior of a compact layer, consequently it is thought that elution can be reduced to altitude.
[0023] dimethylacetamide (henceforth DMAC), a N-methyl-2-pyrrolidone, dimethyl sulfoxide (henceforth DMSO), dimethylformamide, etc. can be illustrated, and independent as a good solvent of a polysulfone system polymer used by the 1st approach, -- or it is mixed and used. DMAC and/or DMSO are used preferably especially. Moreover, as a poor solvent of a polysulfone system polymer, although water, isopropyl alcohol, ethanol, propyl propylene glycol, tetraethylene glycol, etc. can be illustrated, water is used preferably especially. Although the mixing ratio of the good solvent and poor solvent of this polysulfone system polymer does not generally have ********** since conditions change with the classes or processing temperature of a solvent, it is desirable to use the good solvent of a polysulfone system polymer as 30 - 95 % of the weight. For example, 30 - 60% of the weight of a DMAC water solution, 30 - 60% of the weight of N-methyl pyrrolidone water solution, 50 - 95% of the weight of a DMSO water solution, etc. are used. moreover, the good solvent of a polysulfone system polymer and the poor solvent of a polysulfone system polymer -- independent -- it is not necessary to use it -- each of two sorts or the good solvent beyond it, or a poor solvent -- the mixed solution of mixture is sufficient. Although the temperature of arbitration is sufficient as it, when using the water solution of the good solvent of a polysulfone system polymer, below the boiling point of water is desired on actuation, it is the range where 10-98 degrees C is desirable, processing temperature has still more desirable 30-98 degrees C, and 50-95 degrees C is desirable [temperature].
[0024] The 2nd approach of washing clearance of this invention is the approach of washing the polysulfone system hollow fiber which produced the film with a hot alcohols solvent. The polysulfone system polymer particle which constitutes the film swells, and while PVP incorporated weakly becomes easy to separate, the diffusion rate of PVP becomes large. For this reason, in processing of rinsing or heat rinsing, it is presumed that washing clearance of PVP which is hard to remove is carried out. Therefore, when processing temperature is low, washing removing becomes inadequate, the higher one is desired, but if too high, change of membrane structure will take place and membraneous ability will be changed. For this reason, in this invention, washing processing at 130-160 degrees C is desired. It is 135-155 degrees C preferably, and is 140-150 degrees C still more preferably.
[0025] Although the alcohols solvent which can be used by this invention is the good solvent of PVP and all the things that have a swelling operation to a polysulfone system polymer are raised, the alcohols solvent which has the boiling point or the decomposition point 130 degrees C or more from the simple nature of actuation and equipment is desirable. A glycerol is used preferably especially. Little direction is desirable, and the moisture regain of an alcohols solvent can recommend 5% or less, is desirable, and is still more desirable. [0.5% or less of] [1% or less of] It is not necessary to let the process of rinsing or heat rinsing pass beforehand, and to use PVP which is easy to be removed, and the thing which removed the solvent of a spinning undiluted solution as a polysulfone system hollow fiber which the 1st approach and 2nd approach produced. Even if the solvent of a spinning undiluted solution remains, it is guessed that it is also more effective for washing clearance of PVP to be in the condition that the film expanded.
[0026] Moreover, the 1st approach and 2nd approach can illustrate the following approach as an

art. (1) Make the temperature of arbitration heat this film in the condition of having made the penetrant remover immersed. (2) Make the film immersed in the penetrant remover adjusted to laying temperature. (3) Carry out the shower of the penetrant remover adjusted to laying temperature to the film. (4) Make it run the film in the penetrant remover adjusted to laying temperature. What is necessary is to be possible and just to contact enough the penetrant remover by which the polysulfone system hollow fiber which produced the film in short was adjusted to laying temperature by any approach. By the approach of (1) - (3) which changes with arts and serves as batch operation, 10 minutes or more of the processing time are desirable, and it is still more desirable. [of 30 minutes or more] Moreover, in (4) used as consecutive operation, it is required for the residence time to be 15 seconds or more, and 20 seconds or more are still more desirable. It is desirable to carry out washing clearance of the solvent used after processing by rinsing, heat rinsing, etc. as a matter of course.

[0027] When the internal surface of the polysulfone system hollow filament mold blood purification film of this invention is observed with a scanning electron microscope, the fibrous polysulfone system polymer (fibril) forms the structure where it has gathered together with hollow filament fiber shaft orientations, and there is a gap between fibrils in some places. Between this fibril is torn by the conditions of film production, and that gap becomes large according to them so that it may mention later. In the hollow fiber which has such an internal surface, while surface smooth nature is lost and haemocompatibility worsens, the clearance nature of a solute molecule is also affected bad. For this reason, in the hollow fiber of this invention, a hollow fiber internal surface is expected not to have the torn gap 0.8 micrometers or more.

[0028] It opts for sieving of a solute molecule with solute molecular size and the magnitude of a membranous hole. That is, although a solute molecule smaller than a membranous aperture can penetrate the film, a bigger solute molecule than a membranous aperture cannot be penetrated. Although sieving of a solute molecule breaks out by this principle, when membrane structure is the uneven film and an aperture becomes small in the direction of a film cross section, sieving takes place by the selection detached core as used in the field of this invention. Generally, the selection detached core as used in the field of [by the way a film aperture is small, therefore] this invention of structure with a precise polymer part can be deciphered from the transmission electron microscope image of a film cross section. That is, it asks for the rate (ratio of organized labor) that perform a break and image analysis by fixed width of face, and a polymer part occupies the image of the transmission electron microscope of a film cross section. If this actuation is turned to a hollow fiber outside and performed from the hollow fiber inside, distribution of the ratio of organized labor in the direction of a hollow fiber membrane cross-section will become clear. Pore size distribution was in the film so that it might mention later, but when image analysis of the selection detached core was carried out having used width of face of image analysis as 0.5-1.0 micrometers by this invention in consideration of it, from the highest value of a ratio of organized labor, it was defined as the part in less than 30% of range, and the thickness was measured.

[0029] A membranous fractionation property is explained by the multilayer-structure model. That is, the structure in which the layer of a large number which sliced the film (vertically [as opposed to / Therefore / a film cross section]) to parallel to the film surface carried out the laminating is assumed. A solute molecule is screened for every layer of this, and I think that multistage filtration is performed by the whole film. Although average apertures differ for every layer, since the aperture in the layer has distribution when one layer is taken up, there is not

effectiveness which a solute screens but only the layer of min [aperture / average] can catch the big solute molecule through which the layer to which the average aperture became large a little has also passed. In other words, the solute molecule with which the average aperture has passed through the big place of an aperture in the small layer is fully caught with a hole with size smaller than a solute molecule, although the average aperture became a little large. Therefore, as a selection detached core, even the layer [layer / min / aperture / average] to which it became large a little is effective.

[0030] The thickness of a selection detached core is important for the sharpness of a fractionation property. If a little average aperture tends to be raised and it is going to improve permeability of the clearance matter when a selection detached core is thin, it will become easy to penetrate the albumin which is a useful plasma protein. If distribution of an aperture is in a selection detached core and an average aperture is raised, it will be guessed for the holes which can penetrate albumin according to it also increasing in number. Since there is no another selection detached core which catches the albumin once leaked from the big part of an aperture when a selection detached core is thin, the film will be penetrated as it is. Moreover, also when a structure defect arises in a selection detached core under the effect of slight fluctuation of spinning conditions etc., leak of the amount matter of macromolecules becomes remarkable especially. On the other hand, about membrane structure, when a selection detached core is thick, even if comparatively loose, if the thickness is thick, there will be little leak of albumin, namely, a molecular weight fractionation property will become Sharp. Since the membranous selection detached core is thick as for this, even if albumin penetrates in one layer, it is because the probability which is caught in some layer of a selection detached core, and penetrates the film as a result becomes low. However, since transparency resistance will become large too much if a selection detached core is too thick, in this invention, it is required to be 2 micrometers - 15 micrometers, it is 3 micrometers - 12 micrometers still more preferably, and 5 micrometers - 10 micrometers are more desirable.

[0031] Although it may be in the hollow fiber inside, may be located in a cross-section core, or may be located on both the hollow fiber inside and the hollow fiber outside or any are sufficient as it at a screening efficiency, as for the location of a selection detached core, it is desirable that a selection detached core is in the hollow fiber inside in this invention in order to prevent encroachment on the film of the protein in the blood leading to plugging of a film inner hole generally, since blood is poured by the hollow fiber inside.

[0032] On the occasion of film production of the polysulfone system hollow filament mold blood purification film in this invention, the dryness-and-moisture type film production technique which is a technique generally known from before can be used. That is, a polysulfone system polymer and PVP are first dissolved in a common solvent at both, and a uniform spinning undiluted solution is adjusted. As a common solvent which dissolves such both polysulfone system polymers and PVP, the solvent which consists of a solvent of varieties, such as DMAC, DMSO, a N-methyl-2-pyrrolidone, dimethylformamide, a sulfolane, and dioxane, or the two or more above-mentioned sorts of mixed liquor is mentioned, for example. Moreover, additives, such as water, may be added to a spinning undiluted solution for aperture control.

[0033] Although a big macro void comes to appear notably inside the film when spinning undiluted solution viscosity is too low, in the case of the hollow fiber for blood purification, in the hollow fiber which blood coagulation will become easy to happen during hemodialysis, and will be used for hemodialysis if many such macro voids exist, it is desirable that there is no macro void. As for the macro void said here, the overall diameter says a thing 5 micrometers or

more among the space in which a polymer does not exist within the film. On the other hand, it undiluted solution viscosity becomes high too much, the pressure in front of a spinneret is improved too much, and stable spinning becomes impossible. Therefore, in this invention, 1500 - 6000mPa and a second are required for spinning undiluted solution viscosity, and the range of 2000 - 4000mPa and a second is desirable. With the viscosity said by this invention, a spinning undiluted solution is measured with the viscometer of a rotating type at the spinneret temperature and this temperature under film production conditions.

[0034] Depending on the polysulfone system polymer in the molecular weight of PVP, and a spinning undiluted solution and the concentration of PVP, the temperature of a spinning undiluted solution, etc., as for the viscosity of a spinning undiluted solution, every factor does the serious effect for formation of membrane structure. In this invention, undiluted solution viscosity is adjusted to the above-mentioned range by choosing the raw material to be used appropriately and setting up the conditions of concentration and temperature. Since membranous formation will become difficult if too few, film reinforcement becomes weak too much or phenomena, like an aperture will worsen [spinning nature] too much small if many [too] arise, as for the addition of polysulfone system polymer system resin, it is desirable that it is 15 - 20 % of the weight, and it is still more desirable that it is 16 - 19 % of the weight. However, what is necessary is it not to be absolute that it is this range, and to be also able to enlarge making it smaller than this range depending on the description of the hollow fiber made into the object, and just to choose the optimal combination suitably, since the shape of membranous changes also by changing other spinning conditions.

[0035] The object which adds PVP to a spinning undiluted solution is making PVP remain in a hollow fiber and giving a hydrophilic property to the film. Therefore, the molecular weight of PVP to be used is important. That is, when the molecular weight of PVP is too small, since this PVP is easily eluted from the film, in order to make PVP required to give a hydrophilic property to a hollow fiber remain in a hollow fiber, it is necessary to add a lot of PVP to a spinning undiluted solution at the time of the coagulation of a spinning undiluted solution, and washing of the obtained hollow fiber. for this reason, K-value with which the one where molecular weight is larger is desirable for raising the survival rate to the hollow fiber of PVP, and is defined as it by the degree type -- 88-95 -- 89-94 are preferably good.

[0036]

[Formula 1]

$$K\text{値} = \frac{\sqrt{300C\log Z + (C + 1.5C\log Z)^2} + 1.5C\log Z - C}{0.15C + 0.003C^2}$$

Here, Z is the rate of relative viscosity of the solution of concentration C, and C is the concentration of % (weight/capacity).

[0037] The relative amount of the polysulfone system polymer in a spinning undiluted solution and PVP is very important when determining the internal-surface PVP concentration of the hollow fiber obtained. The ratio of the absolute magnitude of the polysulfone system polymer which exists in the coagulation side by contact of the liquid in hollow and a spinning undiluted solution in the internal surface of a hollow fiber in order that rapid coagulation may start, and PVP is because it is fixed to an internal surface as it is. When there are too few weight ratios of PVP to the polysulfone system polymer in a spinning undiluted solution, surface PVP concentration does not go up. When there are too many weight ratios of PVP, membranous reinforcement becomes weak and it becomes impossible moreover, to disregard the elution

volume of PVP from the film to a polysulfone system polymer. then, the weight ratio of PVP [as opposed to / when it is going to make PVP concentration of a hollow filament internal surface 30% - 45%, with the reinforcement beyond the need maintained / the polysulfone system polymer in a spinning undiluted solution] -- 0.25 thru/or 0.5 -- it is preferably required 0.3 thru/or 0.48, and to be 0.35 thru/or 0.45 still more desirably.

[0038] That what is necessary is for the liquid in hollow to be able to use the coagulation liquid which made water or water the subject, and just to decide the presentation etc. according to the membraneous ability of the hollow fiber made into the object, although there is no ********** generally, generally the mixed solution of the solvent and water which were used for the spinning undiluted solution is used suitably. For example, although 0 - 60% of the weight of a DMAC water solution etc. is used, it is especially desirable that it is 0 - 40 % of the weight. It rolls round, after making the water installed in the spinning port lower part after extruding simultaneously the liquid in hollow for facing producing a hollow fiber and making said spinning undiluted solution and this spinning undiluted solution solidify from this spinning port using the duplex spinning port of a tube in orifice mold in the air and making it run the 20-80cm free-running section immerse and solidify into the coagulation bath made into a subject.

[0039] the rate of a spinning draft as used in the field of this invention -- the annular slit of the duplex spinning port of a tube in orifice mold -- it is the value which is the ratio of regurgitation linear velocity in case a spinning undiluted solution is breathed out, and the rolling-up rate of a hollow fiber, and broke the rolling-up rate by regurgitation linear velocity of a spinning undiluted solution from the mouthpiece. In the case of the low rate of a spinning draft, it is necessary to make slit width of a spinneret that much narrow. In the case of the hollow fiber for blood purification, the range of the thickness usually used is 20-60 micrometers. For this reason, when the rate of a spinning draft is low, since the regurgitation linear velocity of an undiluted solution will increase and the pressure loss in a spinneret will become large if spinning speed is raised, spinning tends to become instability. Moreover, since the regurgitation nonuniformity of an undiluted solution arises, the variation in turbulence, permeable ability, and the solute transparency engine performance also becomes [membrane structure] large. Furthermore, since slit width is narrow, problems, like that the alignment of a spinneret becomes difficult and the creation of a spinneret itself becomes difficult and it becomes high cost are pointed out. On the contrary, while it rolls round to the regurgitation linear velocity of the undiluted solution from a spinneret, and a hollow filament internal surface will solidify directly under a spinneret when a rate is too quick if the rate of a spinning draft is too high namely, it becomes the configuration by which the compact layer of a film internal surface was tore by being pull strongly, and since it becomes easy to generate the hole which has an extraordinarily big aperture, the leak problem of the albumin which is useful protein arises. This problem is stopping undiluted solution viscosity low by making high temperature of the spinning undiluted solution into which the presentation of a spinning undiluted solution is changed etc., and a certain extent is not enough although it is improvable. Therefore, in this invention, 1.1-1.9 are required for the rate of a spinning draft, and it is desirable that it is the range of 1.1-1.5.

[0040] The regurgitation linear velocity of the undiluted solution said here is linear velocity in case a spinning undiluted solution is breathed out from a spinneret at the time of spinning, and is the value which broke the amount of discharge flow of the spinning undiluted solution per unit time amount by the undiluted solution regurgitation cross section of a spinneret. If the regurgitation linear velocity of an undiluted solution becomes large, the regurgitation nonuniformity of an undiluted solution will become large, the hole which has a big aperture by

membranous structure nonuniformity will form, and leak of albumin will arise. At this invention, the regurgitation linear velocity of an undiluted solution needs to be 90 or less m/min, it is desirable that they are 70 or less m/min, and it is more more desirable still that they are 60 or less m/min.

[0041] In order to control a selection detached core, a film production process as shown below is important. First, as a result of coagulation's progressing gently since the coagulation force becomes weak if the class and concentration of the liquid in hollow are important and make high solvent concentration in the liquid in hollow, precise condensation structure cannot be taken but a selection detached core becomes **** structure. Next, if the viscosity of a spinning undiluted solution is important and viscosity is high, migration of a polysulfone system polymer will be suppressed at the time of coagulation, and a selection detached core will become thick compared with the case where viscosity is low, under these conditions. Depending on the concentration of the polysulfone system polymer in the molecular weight of a hydrophilic macromolecule, and a spinning undiluted solution, and a hydrophilic macromolecule, the temperature of a spinning undiluted solution, etc., as for the viscosity of a spinning undiluted solution, every factor does the serious effect for formation of a selection detached core. Moreover, it is better to raise the rate of a spinning draft by the factor also with an important spinning draft, in order to give a thick selection detached core. Although there is a solvent used for the distance of the free-running section from a spinneret to a coagulation bath, spinneret size, the temperature of a coagulation bath, a presentation and spinning speed, and a spinning undiluted solution in addition to this, it is necessary to set up the factor which affects formation of a selection detached core in consideration of balance with the penetrable ability of a solute, the object, etc.

[0042] After treatment of the hollow fiber which spinning was carried out as mentioned above and rolled round is carried out by the well-known approach. That is, after removing a solvent and superfluous PVP by washing by hot water etc. and giving a glycerol if needed, dry heat desiccation is carried out. Moreover, after rolling round a hollow fiber, after treatment is not carried out, but the approach of rolling round, after carrying out dry heat desiccation, washing by hot water etc. and is also within the limits of this invention, an important thing adjusts spinning undiluted solution viscosity to 1500 - 6000mPa and a second by this invention, the regurgitation linear velocity from a spinneret is the conditions of 90 or less m/min, and it is making the rate of a spinning draft or less into 1.1 to 1.9.

[0043]

[The mode of implementation of invention] Although an example and the example of a comparison are used for below and this invention is explained to it at a detail, thereby, this invention is not limited at all. The amount of water penetration and sieve multiplier in this invention are measured as follows. That is, assembly molding of the mini module (25cm of effective length) which consists of 100 dried polysulfone system selection transparency hollow fibers was carried out, and the amount of water penetration was measured in the unit of ml/Hr/m2 / mmHg with the Floe process also as that of the flow and pressure requirement of 200mmHg. Then, beta2-MG and the sieve multiplier of albumin were further measured using cow plasma. Using ORIENTECTENSILON;RTC -1210, yarn reinforcement was pulled until it fractured the hollow fiber, and it made reinforcement maximum load which took then.

[0044]

[Example 1] The uniform spinning undiluted solution which consists of the polysulfone resin (Amoco performance products company make, P-1700) 17 weight section, the polyvinyl-pyrrolidone (BASF make, K-92) 7 weight section, and the DMAC76 weight section was created.

This spinning undiluted solution viscosity was 3400 mPa-s at 65 degrees C. having kept this spinning undiluted solution at 65 degrees C -- the liquid in hollow of 15%DMAC -- the slit width of 59.5 micrometers -- annular -- from the mouthpiece, it was immersed in discharge and underwater [which were prepared caudad 60cm / 55-degree C], and rolled round at the rate of 70 m/min. Since the discharge quantity of a spinning undiluted solution was adjusted so that the hollow fiber thickness at the time of desiccation might be doubled with 45 micrometers, the regurgitation linear velocity of an undiluted solution became 49.3 m/min, and the rate of a draft was 1.42. The shower of 40% of the weight of the DMAC water solution which warmed the acquired hollow fiber bundle at lowering and 85 degrees C was carried out for 80 minutes. Then, hot water washing was carried out at 90 degrees C, it was immersed in the glycerol water solution 20%, and the glycerol was made to adhere. Subsequently, hot air drying was carried out at 75 degrees C for 11 hours. Then, the hollow fiber was made immersed in the water solution in which 600 ppm of sodium disulfite and 300 ppm of sodium carbonates were dissolved, the gamma ray of 25kGy was irradiated, and the polysulfone system blood purification film was obtained. The osmium tetroxide water solution dyed the obtained hollow fiber, embedding was carried out with the epoxy resin after dehydration, about 60nm ultrathin section was created after hardening using ultramicrotome, and TEM (JEM2000FX) observation was performed. The ratio of organized labor was measured towards the outside-surface side at intervals of 0.7 micrometers using the obtained TEM image with image-analysis equipment (IP-1000: Asahi Chemical Co., Ltd. make) from the hollow fiber internal-surface side. A measurement result and a membranous assessment result are shown in a table 1. Moreover, the situation of the internal surface of this film is shown in drawing 1 . There is no torn structure and it has become a smooth front face.

[0045]

[Example 2] The polysulfone system blood purification film was obtained like the example 1 except having carried out the shower of the 130-degree C glycerol for extract washing of a hollow fiber for 3 hours instead of 80 degrees C and the shower for 80 minutes in 40%DMAC water solution. The obtained result is shown in a table 1.

[Example 3] The polysulfone system blood purification film was obtained like the example 1 except not performing extract washing by the shower for 80 degrees C and 80 minutes in 40%DMAC water solution. The obtained result is shown in a table 1.

[0046]

[Example 4] The uniform spinning undiluted solution which consists of the polysulfone resin (Amoco performance products company make, P-1700) 17 weight section, the polyvinyl-pyrrolidone (BASF make, K-89) 7 weight section, and the DMAC76 weight section was created. This spinning undiluted solution viscosity was 1650 mPa-s at 80 degrees C. having kept this spinning undiluted solution at 80 degrees C -- the liquid in hollow of 15%DMAC -- the slit width of 59.5 micrometers -- annular -- it was immersed in discharge and underwater [which were prepared caudad 60cm / 55-degree C] from the mouthpiece, and rolled round by 70 m/min. After that, the polysulfone system blood purification film was obtained like the example 1. The obtained result is shown in a table 1.

[0047]

[Example 5] The uniform spinning undiluted solution which consists of the polysulfone resin (Amoco performance products company make, P-1700) 16 weight section, the polyvinyl-pyrrolidone (BASF make, K-89) 7.8 weight section, and the DMAC76.2 weight section was created. This spinning undiluted solution viscosity was 2500 mPa-s at 70 degrees C. having kept this spinning undiluted solution at 70 degrees C -- the liquid in hollow of 15%DMAC -- the slit

width of 59.5 micrometers -- annular -- it was immersed in discharge and underwater [which were prepared caudad 60cm / 55-degree C] from the mouthpiece, and rolled round by 70 m/min. After that, the polysulfone system blood purification film was obtained like the example 1. The obtained result is shown in a table 1.

[0048]

[Example 6] The uniform spinning undiluted solution which consists of the polysulfone resin (Amoco performance products company make, P-1700) 17 weight section, the polyvinyl-pyrrolidone (BASF make, K-92) 5.5 weight section, and the DMAC78.5 weight section was created. This spinning undiluted solution viscosity was 2400 mPa-s at 50 degrees C. having kept this spinning undiluted solution at 50 degrees C -- the liquid in hollow of 15%DMAC -- the slit width of 59.5 micrometers -- annular -- it was immersed in discharge and underwater [which were prepared caudad 60cm / 55-degree C] from the mouthpiece, and rolled round by 70 m/min. After that, the polysulfone system blood purification film was obtained like the example 1. The obtained result is shown in a table 1.

[0049]

[Example 7] The uniform spinning undiluted solution which consists of the polysulfone resin (Amoco performance products company make, P-1700) 17 weight section, the polyvinyl-pyrrolidone (BASF make, K-89) 6.3 weight section, and the DMAC76.7 weight section was created. This spinning undiluted solution viscosity was 2820 mPa-s at 55 degrees C. having kept this spinning undiluted solution at 55 degrees C -- the liquid in hollow of 15%DMAC -- the slit width of 59.5 micrometers -- annular -- it was immersed in discharge and underwater [which were prepared caudad 60cm / 55-degree C] from the mouthpiece, and rolled round by 70 m/min. After that, the polysulfone system blood purification film was obtained like the example 1. The obtained result is shown in a table 1.

[0050]

[The example 1 of a comparison] The polysulfone system hemodialysis film was obtained like the example 6 except not irradiating a gamma ray. The obtained result is shown in a table 1.

[The example 2 of a comparison] It was underwater immersed instead of making a hollow fiber immersed in the water solution in which 600 ppm of sodium disulfite and 300 ppm of sodium carbonates were dissolved, and the polysulfone system hemodialysis film was obtained like the example 6 except having irradiated the gamma ray of 50kGy. The obtained result is shown in a table 1.

[0051]

[The example 3 of a comparison] a spinning undiluted solution -- the liquid in [15% of] hollow -- the slit width of 59.5 micrometers -- annular -- instead of carrying out the regurgitation from a mouthpiece -- the slit width of 125 micrometers -- annular -- the polysulfone system blood purification film was obtained like the example 1 except having made it breathe out from a mouthpiece. The obtained result is shown in a table 1. Moreover, the rate of a draft was 3.2 at this time. The internal surface of this film has structure torn greatly under the effect of a draft, and shows that situation to drawing 2 .

[The example 4 of a comparison] a spinning undiluted solution -- the liquid in hollow of 15%DMAC -- the slit width of 59.5 micrometers -- annular -- instead of carrying out the regurgitation from a mouthpiece -- the slit width of 50 micrometers -- annular -- the polysulfone system blood purification film was obtained like the example 1 except having made it breathe out from a mouthpiece. The obtained result is shown in a table 1. Moreover, the rate of a draft was 1.0 at this time. Although there is no structure which was torn since the internal surface of

this film has the low draft, it is the effect considered to be the regurgitation nonuniformity of an undiluted solution, and structure nonuniformity is seen. The situation is shown in drawing 3 .
[0052]
[The example 5 of a comparison] The uniform spinning undiluted solution which consists of the polysulfone resin (Amoco performance products company make, P-1700) 17 weight section, the polyvinyl-pyrrolidone (BASF make, K-92) 3.5 weight section, and the DMAC79.5 weight section was created. This spinning undiluted solution viscosity was 1250 mPa-s at 50 degrees C. having kept this spinning undiluted solution at 50 degrees C -- the liquid in hollow of 15%DMAC -- the slit width of 59.5 micrometers -- annular -- it was immersed in discharge and underwater [which were prepared caudad 60cm / 55-degree C] from the mouthpiece, and rolled round by 70 m/min. After that, the polysulfone system blood purification film was obtained like the example 1. The obtained result is shown in a table 1.
[0053]
[A table 1]
表1

	バルクPVP (%)	ESCA:PVP (%)	溶出PVP (mg/m2)	Alb SC (%)	β2−Mg (%)	透水 (＊)	残血	緻密層 (μm)	引き裂き	強度 (g/hf)	可溶性PVP (mg/g-HF)
実施例1	7.0	38	0.25	0.003	0.64	210	○	10.5	無し	17.1	8.0
実施例2	7.1	38	0.26	0.003	0.64	205	○	10.6	〃	17.2	8.3
実施例3	8.9	39	1.01	0.002	0.55	175	○	11.2	〃	17.1	11.9
実施例4	5.0	35	0.27	0.004	0.68	287	○	4.8	〃	19.2	6.9
実施例5	8.1	44	0.25	0.004	0.61	165	○	8.2	〃	16.3	9.6
実施例6	4.5	30	0.41	0.005	0.70	514	○	9.2	〃	19.8	7.8
実施例7	5.5	33	0.30	0.002	0.68	222	○	7.5	〃	19.0	7.8
比較例1	4.8	31	2.20	0.003	0.63	229	○	9.5	〃	19.8	43.0
比較例2	4.8	31	0.10	0.003	0.67	209	×	9.5	〃	19.8	0.2
比較例3	4.6	32	0.25	0.010	0.69	255	×	9.3	有り	19.8	8.0
比較例4	7.3	38	0.28	0.009	0.68	245	○	9.2	ムラ	17.0	8.1
比較例5	3.2	24	0.95	0.011	0.85	702	×	6.8	〃	21.2	2.0

(＊)ml／Hr／m2／mmHg

[0054] Residual blood assessment was carried out about the hollow fiber of examples 1-7 and the examples 1-5 of a comparison. That is, 120 hollow fibers of 16cm length were constructed to the module, and 20ml of physiological salines washed. Then, the blood taken out from the dog carotid artery through the peristaltic pump was shunted toward the hollow filament inside ten by 2ml flow rate for /. After extruding blood by 5ml of physiological salines, the module was disassembled and the degree of residual blood was evaluated. Consequently, by the hollow filament of the examples 2 and 3 of a comparison, and 5**, although residual blood was accepted, it remained [whether there is almost any residual blood and] in the hollow fiber of the other examples of a comparison, and an example a little.

DESCRIPTION OF DRAWINGS

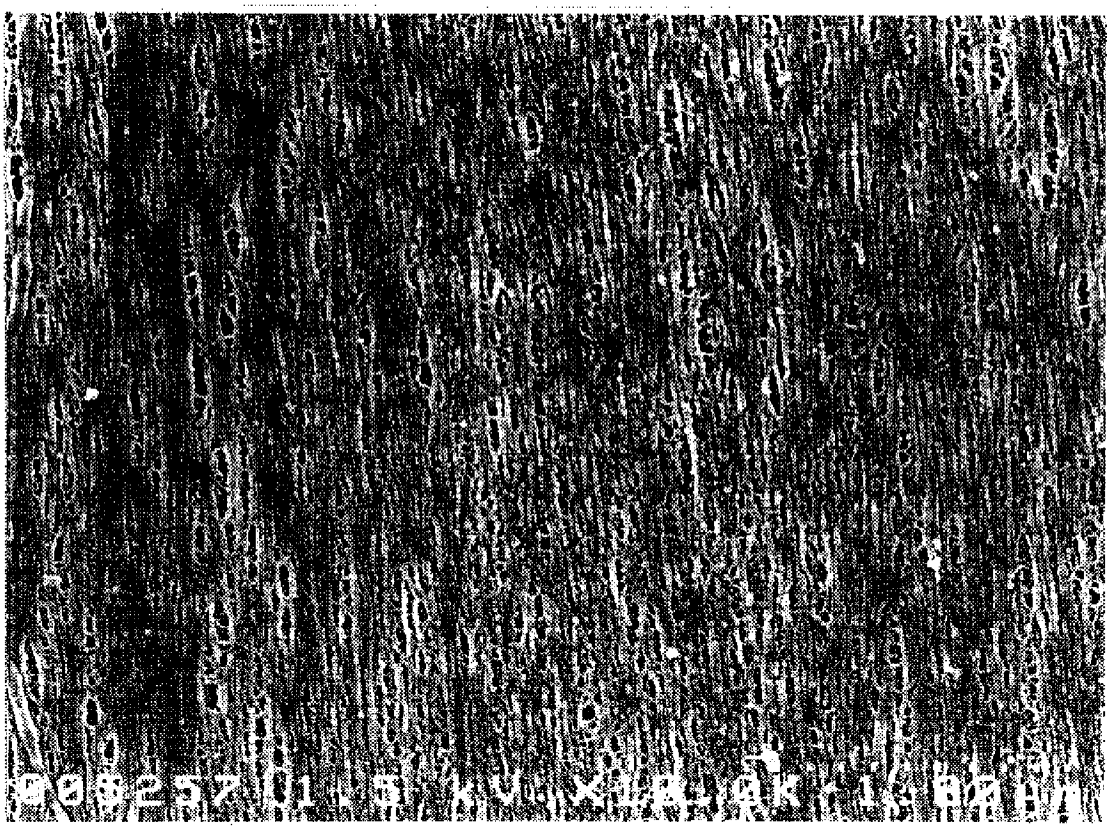
[Brief Description of the Drawings]
[Drawing 1] It is the image which observed the internal surface of the hollow fiber of an example 1 with the scanning electron microscope (upper case: 10000 times, lower-berth:30000 time). An

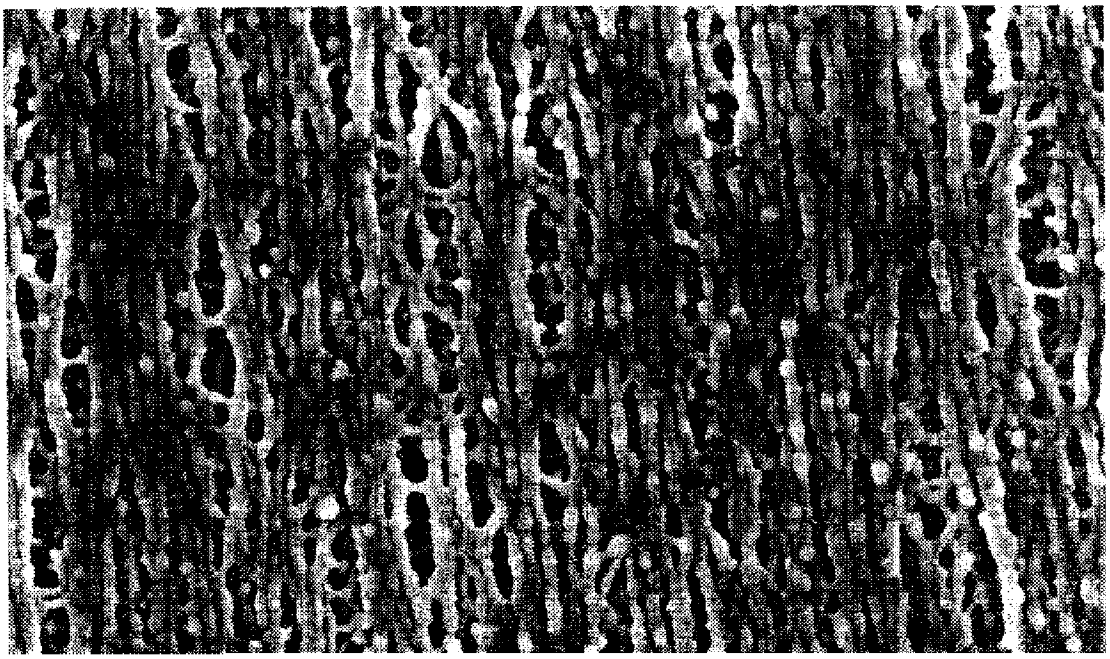
internal surface is smooth and it is observed that fibrils have gathered together with hollow filament fiber shaft orientations.
[Drawing 2] It is the image which observed the internal surface of the hollow fiber of the example 3 of a comparison with the scanning electron microscope (upper case: 10000 times, lower-berth:30000 time). An about 2-micrometer gap which was torn is shown in an internal surface.
[Drawing 3] It is the image which observed the internal surface of the hollow fiber of the example 4 of a comparison by one 1000 times the scale factor of this with the scanning electron microscope. Structure nonuniformity is seen under the effect considered to be the regurgitation nonuniformity of an undiluted solution. The image expanded by 15000 times, respectively is shown in the middle and the lower berth, using a dense part as b using as a the part to which between fibrils is coarse.

DRAWINGS

[Drawing 1]

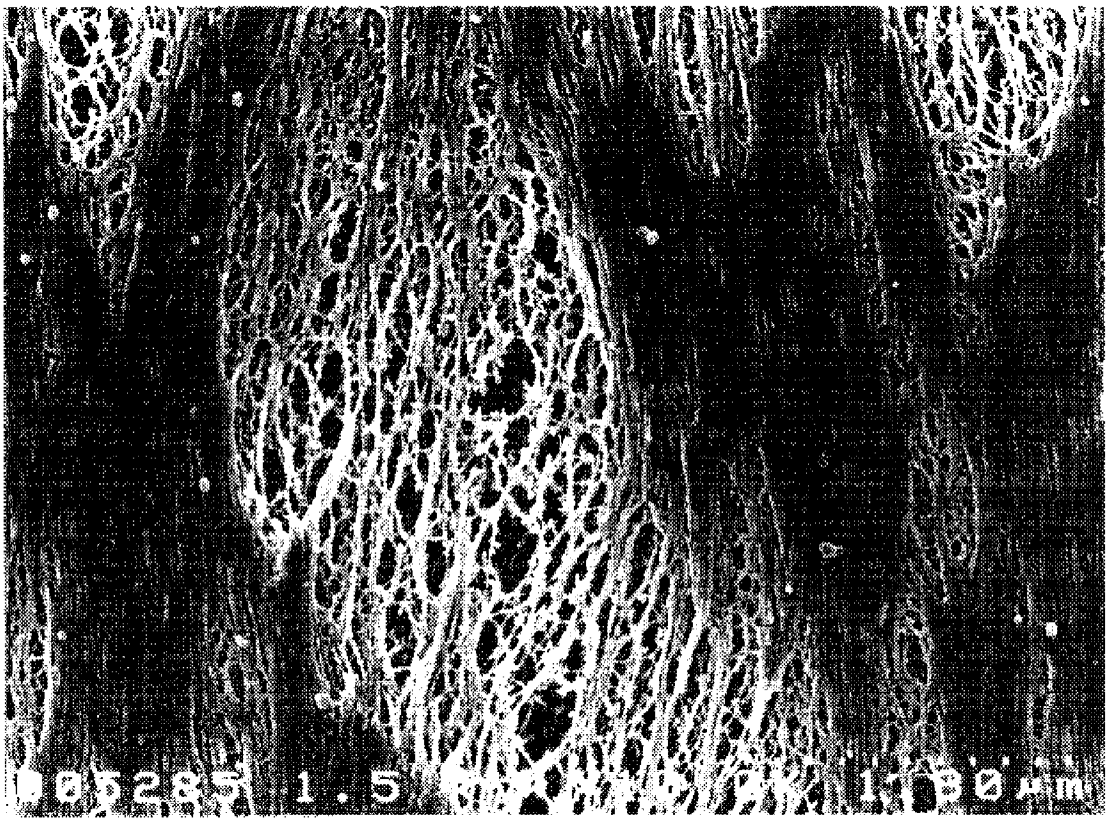
図面代用写真

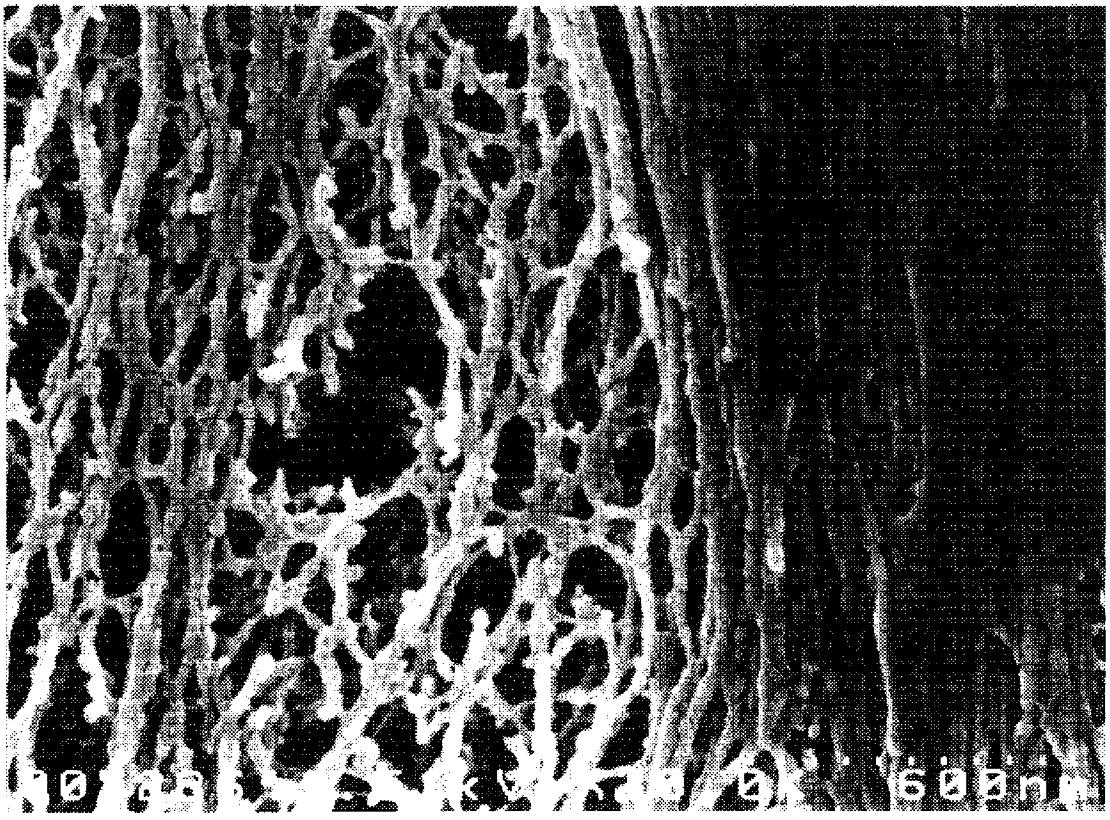




[Drawing 2]

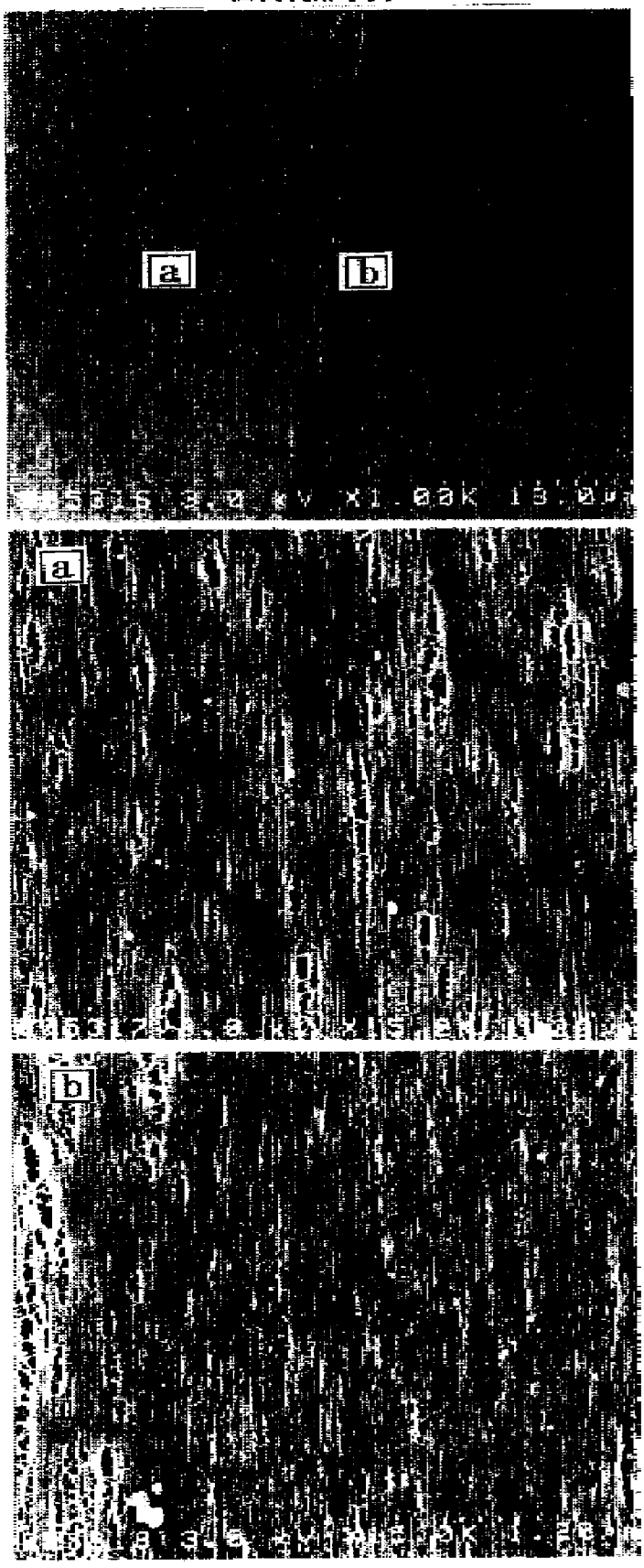
図面代用写真





[Drawing 3]

図面代用写真



[Translation done.]